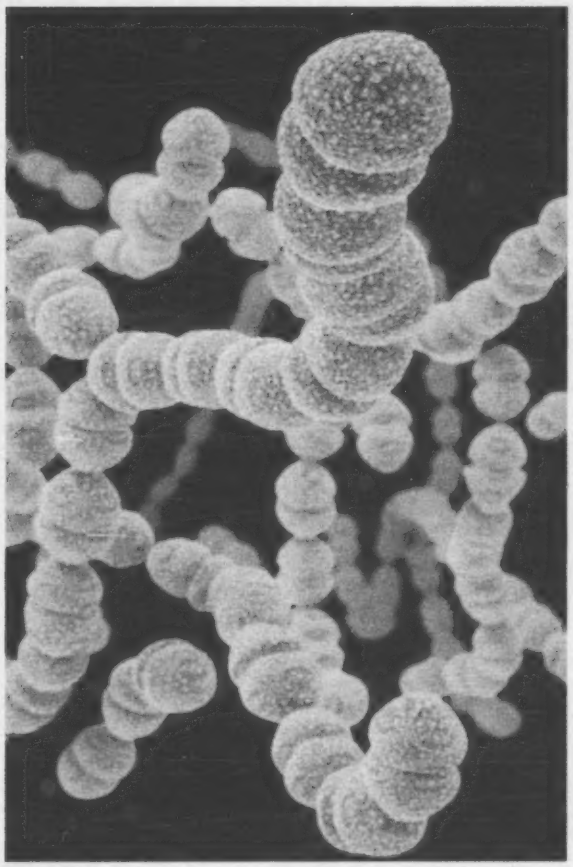
April 7, 2016 • Volume 42-4

CCDR

CANADA COMMUNICABLE DISEASE REPORT

VACCINE-PREVENTABLE DISEASES



Research

Northern populations in Canada are at increased risk of invasive bacterial disease 74

There are ways to improve the tracking of invasive pneumococcal disease 81

Links

Updates on vaccines for malaria, anthrax and dengue 98

Public Health Agency of Canada | Agence de la santé publique du Canada

Canada

CCDR
CANADA COMMUNICABLE DISEASE REPORT

The Canada Communicable Disease Report (CCDR) is a bilingual, peer-reviewed, open-access, online scientific journal published by the Public Health Agency of Canada (PHAC). It provides timely, authoritative and practical information on infectious diseases to clinicians, public-health professionals, and policy-makers to inform policy, program development and practice.

Editorial Office

Editor-in-Chief
Patricia Huston, MD, MPH

Managing Editor
Mylène Poulin, BSc, BA

Production Editor
Wendy Patterson

Editorial Assistants
Diane Staynor
Jacob Amar

Copy Editors
Diane Finkle-Perazzo
Joanna Odrowaz
Lise Lévesque

Contact Us

ccdr-rmtc@phac-aspc.gc.ca
613.301.9930

Photo Credit

Credit: Microphotograph of *Streptococcus pneumoniae* bacteria. Center for Disease Control. http://wwwnc.cdc.gov/travel/diseases/pneumococcal-disease-streptococcus-pneumoniae

CCDR Editorial Board

Michel Deilgat, CD, MD, MPA, CCPE
Centre for Foodborne, Environmental and Zoonotic Infectious Diseases
Public Health Agency of Canada

Catherine Dickson, MDCM, MSc
Resident, Public Health and Preventive Medicine University of Ottawa

Jennifer Geduld, MHSc
Centre for Emergency Preparedness and Response
Public Health Agency of Canada

Judy Greig, RN, BSc, MSc
Laboratory for Foodborne Zoonoses
Public Health Agency of Canada

Judy Inglis, BSc, MLS
Office of the Chief Science Officer
Public Health Agency of Canada

Maurica Maher, MSc, MD, FRCPC
National Defence

Mohamed A. Karmali, MB ChB, FRCPC
Assistant Deputy Minister's Office
Public Health Agency of Canada

Julie McGihon
Public Health Strategic Communications Directorate
Public Health Agency of Canada

Robert Pless, MD, MSc
Centre for Immunization and Respiratory Infectious Diseases
Public Health Agency of Canada

Hilary Robinson, MB ChB, MSc, FRCPC
Centre for Public Health Infrastructure
Public Health Agency of Canada

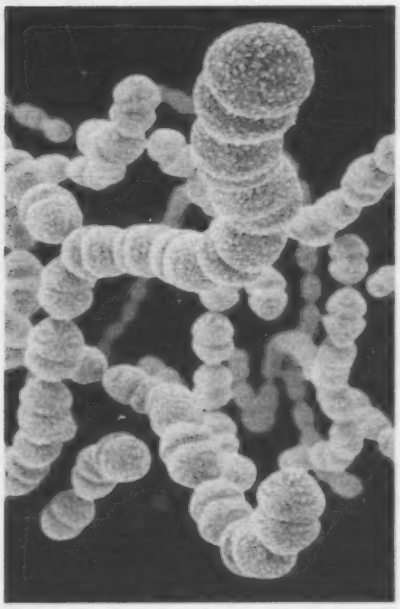
Rob Stirling, MD, MSc, MHSc, FRCPC
Centre for Immunization and Respiratory Infectious Diseases
Public Health Agency of Canada

Jun Wu, PhD
Centre for Communicable Diseases and Infection Control
Public Health Agency of Canada

ISSN 1481-8531 Pub.150005

CCDR
CANADA COMMUNICABLE DISEASE REPORT

VACCINE-PREVENTABLE DISEASES



INSIDE THIS ISSUE

SURVEILLANCE

Invasive bacterial diseases in Northern Canada, 2006-2013 — 74

Li YA, Martin I, Tsang R, Squires SG, Demczuk W, Desai S

EVALUATION

Evaluation of the enhanced Invasive Pneumococcal Disease Surveillance System (eIPDSS) pilot project — 81

Wijayasri S, Li YA, Squires SG, Martin I, Demczuk W, Mukhi S

OUTBREAK REPORT

Outbreak of Shigella sonnei in Montréal's ultra-Orthodox Jewish community, 2015 — 86

Pilon PA, Camara B, Bekal S

RECOMMENDATION

Interim recommendations for the reporting of extensively drug resistant and pan-drug resistant isolates of Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter spp. and Stenotrophomonas maltophilia — 91

German GJ, Jamieson FB, Gilmour M, Almohri H, Bullard J, Domingo MC, Fuller J, Girouard G, Haldane D, Hoang L, Levett PN, Longtin J, Melano R, Needle R, Patel SN, Rebbapragada A, Reyes RC, and Mulvey MR

ID NEWS

Malaria vaccine — 98

Anthrax vaccine — 99

Dengue vaccine — 99

UPCOMING — 100

SURVEILLANCE

Invasive bacterial diseases in Northern Canada, 2006–2013

Li YA[1*], Martin I[2], Tsang R[2], Squires SG[1], Demczuk W[2], Desai S[1]

Affiliations

[1]Infectious Diseases Prevention and Control Branch, Public Health Agency of Canada, Ottawa, ON

[2]National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, MB

***Correspondence:** anita.li@phac-aspc.gc.ca

Abstract

Background: Northern populations are known to be at a higher risk of developing invasive bacterial diseases (IBDs) compared with the rest of Canada. Since the last published study that described IBDs in Northern Canada, a number of vaccines against some bacterial pathogens have been introduced into the routine childhood immunization schedule.

Objective: To describe the epidemiology of IBDs in Northern Canada from 2006 to 2013 and compare their incidences in the North to the rest of Canada.

Methods: Data for 5 IBDs (invasive pneumococcal disease [IPD], invasive *Haemophilus influenzae disease* [Hi], invasive Group A streptococcal disease [iGAS], invasive meningococcal disease [IMD] and invasive Group B streptococcal disease [GBS]) were extracted from the International Circumpolar Surveillance (ICS) program and the Canadian Notifiable Diseases Surveillance System. Incidence rates were calculated per 100,000 population per year.

Results: During the study period, the incidence rates of IPD ranged from 16.84–30.97, iGAS 2.70–17.06, Hi serotype b 0–2.78, Hi non-b type 2.73–8.53, and IMD 0–3.47 per 100,000 population. Except for IMD and GBS, the age-standardized incidence rates of other diseases in Northern Canada were 2.6–10 times higher than in the rest of Canada. Over the study period, rates decreased for IPD ($p = 0.04$), and iGAS ($p = 0.01$), and increased for Hi type a (Hia) [$p = 0.004$]. Among IPD cases, the proportion of pneumococcal conjugate vaccine (PCV7) serotypes decreased ($p = 0.0004$) over the study period. Among Hi cases, 69.8% were Hia and 71.6% of these were in children under than 5 years. Of 13 IMD cases, 8 were serogroup B and 2 of them died. In Northern Canada, the incidence of IPD, iGAS and Hi was 2.6 to 10 times higher than the rest of Canada.

Conclusion: Northern populations in Canada, especially infants and seniors among First Nations and Inuit, are at higher risk of IPD, Hi and iGAS than the rest of Canada. Hia is the predominant serotype in Northern Canada.

Suggested citation: *Li YA, Martin I, Tsang R, Squires SG, Demczuk W, Desai S. Invasive bacterial diseases in Northern Canada, 2006–2013. Can Comm Dis Rep 2016;42:74-80.*

Introduction

Established in 1999, the International Circumpolar Surveillance (ICS) program is a population-based infectious disease surveillance network of circumpolar countries including United States, Canada, Greenland, Iceland, Norway, Sweden, Finland and Russia (1). In Canada, Northern regions (Yukon, Northwest Territories, Nunavut, Labrador, and Quebec Cree and Nunavik) and a network of laboratories, including three reference laboratories (the National Centre for Streptococcus [NCS] (1999–2009), the Laboratoire de santé publique du Québec [LSPQ], and the National Microbiology Laboratory [NML]) participate in the ICS program. ICS has been monitoring invasive disease caused by *Streptococcus pneumoniae* (invasive pneumococcal disease, IPD) since 1999 and invasive diseases caused by *Streptococcus pyogenes* (invasive Group A streptococcal disease, iGAS), *Streptococcus agalactiae* (Group B streptococcal disease, GBS), *Haemophilus influenzae* (Hi) and *Neisseria meningitidis* (invasive meningococcal disease, IMD) since 2000.

The demography of Northern Canada differs from the rest of the country. In 2013, the population of Northern Canada was estimated to be 155,666, about 0.4% of the Canadian population. However, the proportion of self-identified Indigenous people (First Nations, Métis or Inuit) was approximately 60% compared to about 4% in Canada overall. Northern populations, and especially Indigenous peoples, have higher rates of invasive bacterial diseases (IBDs) compared with the rest of Canada (2–6).

The last published study describing IBDs in Northern Canada included data from 1999 to 2005 (5). Since then, a number of vaccines against some bacterial pathogens have been introduced into the routine childhood immunization schedule. In Canada, the National Advisory Committee on Immunization (NACI) recommends vaccines and their schedules, but the implementation of vaccine programs varies among provinces and territories. For IPD, routine infant vaccine programs for 7-valent pneumococcal conjugate vaccine (PCV7) began in 2002 and were fully implemented across Northern Canada by January 2006 (7). The IPD vaccine programs began replacing PVC7 with 10-valent pneumococcal conjugate vaccine (PCV10) in 2010. By January 2011, all six regions were using 13-valent pneumococcal conjugate vaccine (PCV13) in their infant IPD vaccine programs. The 23-valent pneumococcal polysaccharide vaccine (PPV23) is used for targeted populations such as people aged 65 years and over and those at risk for IPD (8). Routine infant vaccine programs for Hi type b have been implemented since 1997 (8). For IMD, routine infant vaccine programs of meningococcal C conjugate vaccine (MenC) [9] have been implemented in all six regions as of 2007.

The objective of this report is to describe the epidemiology of IBDs in Northern Canada from 2006 to 2013 and compare their incidences in the North to the rest of Canada.

Methods

Epidemiological data

Surveillance data for Northern Canada and the rest of the country were extracted from ICS and the Canadian Notifiable Diseases Surveillance System (CNDSS), respectively, with disease onset between January 1, 2006 and December 31, 2013. Only cases that met the national case definitions (10) were included. ICS regional coordinators complete disease-specific Bacterial Disease Surveillance Forms (BDSFs) for cases that meet the national case definitions (10) and then collate and review laboratory information. Data included within the BDSF include non-nominal demographic information, clinical information, outcomes, risk factors and immunization history. Completed BDSFs and laboratory reports are sent to the Public Health Agency of Canada using a secure process. CNDSS receives aggregated data containing basic non-nominal demographic information from provinces and territories annually.

Laboratory data

Invasive isolates were submitted to NML, NCS (2006–2009) or LSPQ for characterization. Serotyping of *S. pneumoniae* using the Quellung reaction was performed using commercial pool, group, type and factor antisera from SSI Diagnostica, Statens Serum Institut, Copenhagen, Denmark (11,12). The *emm* sequence types for iGAS isolates were determined using the methodology recommended by the United States Centers for Disease Control and Prevention (CDC) [13]. GBS serotypes were determined using commercial latex-agglutinating antisera from SSI Diagnostica (11,12). Serotyping of *H. influenzae* was accomplished using bacterial agglutination test with antisera from Difco Laboratories (BD Diagnostics, Falcon Lakes, New Jersey, USA), and the results were confirmed by polymerase chain reaction (PCR) [14]. Non-typeable strains of Hi were confirmed by 16S ribosomal RNA sequencing (15). Serogrouping of *N. meningitidis* was performed using bacterial agglutination methods (16). All reference laboratories participate in an ongoing ICS quality control program (17).

Population data

General population estimates were obtained from Statistics Canada (18). Because Statistics Canada only provides Indigenous population estimates for 2006 and 2011 census years, aggregated Indigenous (First Nations, Métis or Inuit) population estimates in this report were obtained from territorial/regional statistics departments. Indigenous population estimates for Labrador and Quebec Cree could only be estimated based on 2006 and 2011 census data. Population estimates of separate Indigenous groups were not available for this report. The 1991 Canadian population was chosen as the standard population for age standardization. The population distribution is based on the final post-Census estimates for July 1, 1991, Canadian population, adjusted for census undercoverage. The age distribution of the population has been weighted and normalized (19).

Data used in this report came from public health surveillance and were exempt from research ethics board approval.

Analysis

The demographic data, serotype distributions, as well as clinical characteristics, and immunization status of the IBD cases were examined. Incidence rates for GBS of the newborn were not calculated since annual live births estimates of Northern regions were not available for this report. All incidence rates were per 100,000 population per year. Direct method was used for calculating age-standardized rates. Confidence intervals (CIs) of age-standardized rates were calculated with the method based on the gamma distribution (20). Cases with missing age were excluded from age standardization. The Chi-squared test and Fisher's exact test were used to compare proportions. Poisson regression was used to compare incidence rates and estimate disease trends. Statistical significance was considered at the 95% confidence level. Descriptive and inferential analyses were conducted using Microsoft Excel 2010 and SAS EG 5.1.

Results

Overview

From 2006 to 2013, the total number of confirmed cases reported in Northern Canada was 270 IPD, 110 iGAS, 109 Hi, 13 IMD and 8 GBS of the newborn. The demographic information for cases of each disease is noted in **Table 1**. A total of 46 IBD related deaths were reported.

Table 1: Demographic distributions of invasive bacterial diseases in Northern Canada, by disease, gender and ethnicity, 2006–2013

Disease (total number)	Median age, years (range)[1]	Sex[2] (male/female)	Number of cases (%)			
			Ethnicity[3]			
			First Nations	Inuit	Métis	Non-Indigenous
IPD (N=270)	39 (0–92)	142/127	114 (46)	94 (38)	3 (1)	36 (15)
iGAS (N=110)	41 (0–90)	61/49	50 (48)	44 (42)	0	11 (10)
Hi (N=109)	1 (0–80)	59/50	28 (11)	74 (72)	0	1 (1)
IMD (N=13)	0 (0–56)	5/8	4 (31)	6 (46)	0	3 (23)
GBS (N=8)	0 (0–88)	5/3	3 (38)	4 (50)	0	1 (12)

Abbreviations: GBS, Group B streptococcal disease; Hi, *Haemophilus influenzae*; iGAS, invasive Group A streptococcal disease; IMD, invasive meningococcal disease; IPD, invasive pneumococcal disease
[1] Two cases with unknown age were excluded
[2] One case with unknown sex was excluded
[3] Thirty-five cases with unknown ethnicity were excluded

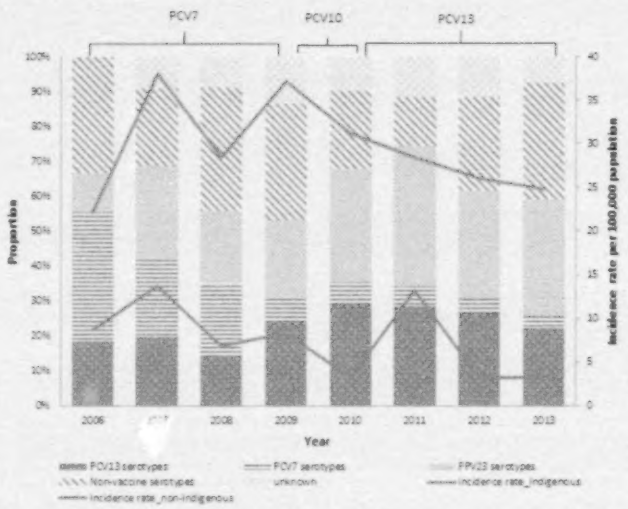
Table 2 shows the annual crude incidence rates of the diseases in Northern regions as well as the age-standardized rates for both Northern regions and the rest of Canada. Except for IMD, age-standardized incidence rates of IPD, iGAS and Hi were significantly higher in Northern regions.

Disease-specific

Invasive pneumococcal disease (IPD)

The age-standardized incidence rate (per 100,000 population) of IPD decreased significantly over the report period ($p = 0.04$) [data not shown]. The age-standardized incidence rates were similar for males (23.55, CI: 19.65–28.10) and females (23.40, CI: 19.31–28.22). The annual incidence rate (per 100,000 population) was highest for infants less than 1 year old (132.68, CI: 88.96–190.55), children aged 1 to 4 years (49.53, CI: 35.70–66.96) and adults 60 years and older (47.85, CI: 35.84–62.59). The average annual incidence rate was 29.51 (range: 22.13–37.12) for those of Indigenous origin and 7.57 (range: 3.18–13.23) for those of non-Indigenous origin, and this difference was significant ($p < 0.0001$) [**Figure 1**].

Figure 1: Invasive pneumococcal disease serotype distribution by year and incidence rates (per 100,000 population) by year and ethnicity in Northern Canada, 2006–2013[1,2]



Abbreviations: IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharides vaccine
[1] PCV7 serotypes: 7 serotypes included in PCV7, i.e., serotype 4, 6B, 9V, 14, 18C, 19F, and 23F; PCV13 serotypes: additional 6 serotypes included in PCV13 compared to PCV7, i.e., serotype 1, 3, 5, 6A, 7F, and 19A; PPV23 serotypes refers to additional 11 serotypes included in PPV23 compared to PCV13, i.e., serotype 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F
[2] A total of 23 cases without ethnicity information were excluded from the incidence calculation

Figure 1 also shows that the proportional distributions of IPD serotypes have changed over the years. The proportion of PCV7 serotypes decreased significantly from 37% (n=10) in 2006 to 4% (n=1) [$p = 0.0004$] in 2013. There have been no cases of PCV7 serotypes under 2 years of age since 2009. Of the cases in this group, the proportion of the additional PCV13 serotypes was 26% before 2011 and 21% after 2011 and the change was not significant ($p = 0.49$). From 2006 to 2013, the most common serotypes were 8 (13.9%), 7F and 19A (6.6% each), 12F (6.0%), and 3, 14, 22F (5.4% each). After 2010, the most common

Table 2: Crude and age-standardized incidence rates (per 100,000 population) of invasive bacterial diseases in Canada, by disease, region and year, 2006–2013[1]

Disease	Crude incidence rates								Age-standardized incidence rates (95% CI)	
									Northern regions[2]	Rest of Canada[2]
	2006	2007	2008	2009	2010	2011	2012	2013	2006–2013	2006–2013
IPD	18.73	30.97	23.20	30.42	20.66	22.96	16.84	17.35	23.59 (20.72–26.80)	8.68 (8.57–8.79)
iGAS	12.49	9.63	17.06	2.70	8.00	7.87	9.07	7.07	10.86 (8.83–13.26)	4.20 (4.12–4.28)
Hib	2.78	0.69	2.05	0.68	0.00	0.66	0.65	0.64	0.89 (0.45–1.71)	0.09 (0.08–0.10)
Hi non-b[3]	7.63	6.88	2.73	6.76	11.33	8.53	7.77	10.92	8.13 (6.26–10.48)[4]	0.95 (0.89–1.01)[4]
IMD	3.47	0	0.68	0.68	0.67	1.31	1.30	0.64	0.87 (0.46–1.63)	0.55 (0.52–0.58)

Abbreviations: CI, confidence interval; Hib, *Haemophilus influenzae* type b; Hi non-b, *Haemophilus influenzae* type OTHER; iGAS, invasive Group A streptococcal disease; IMD, invasive meningococcal disease; IPD, invasive pneumococcal disease
[1] Two invasive Hi disease cases with missing serotype and 1 IPD case with missing age were excluded from the incidence rate calculation
[2] Age-standardized rates and CIs are bolded when the differences between Northern regions and the rest of Canada are significant
[3] For the purpose of comparison, Hi non-b serotypes were grouped into one category to match the national data in Canadian Notifiable Diseases Surveillance System
[4] Age-standardized incidence rates for invasive Hi non-b disease do not include data of 2007–2008

serotypes were 7F (16.5%), 10A (11.4%), 19A, 22F and 33F (7.6% each), and 11A (5.1%).

Of the 44 cases who had been vaccinated with PCV7, the 2 who had PCV7 serotypes were not fully vaccinated at the time of illness. All of the 6 cases who had been vaccinated with PCV10 had non-PVC10 serotypes. Of the 13 cases who had been vaccinated with PCV13, only one had a PCV13 serotype and that case had not been fully vaccinated, i.e., had not received all 4 doses. Of the 70 cases that had PPV23, 20 (29%) were infected with non-vaccine serotype and 5 (7%) with unknown serotype.

In total, 87.4% (n=236) of IPD cases were hospitalized. The most common clinical syndromes (**Table 3**) were pneumonia (68.2%), septicemia/bacteremia (50.4%) and meningitis (7.4%). The overall case-fatality ratio (CFR) was 11.0% (n=28). The majority of the fatal cases were individuals aged 40 and 59 years (46.4%, n=13) and 60 years and older (35.7%, n=10). Individuals in these two age groups with IPD had significantly higher risk for death (CFR=18.1%) than those in younger age groups (CFR=3.9%, $p = 0.0003$). The fatality ratio did not vary between cases in Indigenous and non-Indigenous people ($p = 0.78$). Among 26 fatal cases with serotype information, the majority were PPV23 serotypes (46.2%, serotypes are not included in PCV13) and non-vaccine serotypes (34.6%).

Table 3: Common clinical manifestations and outcomes of cases of invasive pneumococcal disease, invasive Group A streptococcal disease, *Haemophilus influenzae* type b, invasive meningococcal disease and Group B streptococcal disease of the newborn in Northern Canada in 2006-2013[1]

Manifestation and outcome	Number of cases (%)				
	IPD[2] (n=258)	iGAS (n=106)	Hi (n=102)	IMD[3] (n=13)	GBS[3] (n=8)
Septicemia/ Bacteremia	130 (51.2)	42 (40.8)	36 (38.3)	4	6
Meningitis	19 (7.5)	0	24 (25.5)	8	2
Pneumonia	176 (69.3)	17 (16.5)	41 (43.6)	2	2
Empyema	7 (2.8)	7 (6.8)	2 (2.1)	0	0
Septic arthritis	4 (1.6)	11 (10.7)	11 (11.7)	1	0
Necrotizing fasciitis	0	10 (9.7)	0	0	0
Cellulitis	0	33 (32.0)	6 (6.4)	0	0
Death[4]	28 (11.0)	8 (7.8)	8 (8.5)	2 (15.4)	0

Abbreviations: GBS, Group B streptococcal disease; Hi, *Haemophilus influenzae*; iGAS, invasive Group A streptococcal disease; IMD, invasive meningococcal disease; IPD, invasive pneumococcal disease

[1] For each disease, the total percentage of manifestation could be more than 100% due to the multiple manifestations for an individual case

[2] For IPD, pneumonia refers to pneumonia with bacteremia

[3] Due to the small total number of cases, the proportions of manifestation were not calculated for IMD and GBS of the newborn

[4] The total number of cases where outcome information is available was: 254 (IPD), 103 (iGAS), 94 (Hi), 13 (IMD), and 7 (GBS)

Invasive Group A streptococcal disease (iGAS)

The age-standardized annual incidence rate of iGAS decreased significantly ($p = 0.01$) over the report period. Of 110 iGAS cases, 61 were male and 49 female. The age-standardized incidence rates (per 100,000 population) were similar for males (11.86, CI: 8.94–15.51) and females (9.72, CI: 7.07–13.14). The annual incidence rate (per 100,000 population) was the highest for infants under 1 year of age (41.18, CI: 18.83–78.17) and adults aged 60 years and older (47.85, CI: 35.84–62.59), and children aged 1 to 4 years (11.79, CI: 5.66–21.69). The annual incidence rate ranged between 2.25 and 20.44 for Indigenous peoples and between 0 and 6.80 for non-Indigenous people, and the rate was significantly higher for Indigenous peoples ($p < 0.0001$).

Isolates of 74 iGAS cases were *emm* typed, and the most common types were *emm*59 (10.8%), *emm*1 and *emm*91 (9.5% each) and *emm*41 (6.8%). Nighty-two percent (n=101) of cases were hospitalized. As shown in **Table 3**, the most common manifestations were septicemia/bacteremia (39.6%) and cellulitis (31.1%). Pneumonia (16%), septic arthritis (10.4%), necrotizing fasciitis (9.4%) and empyema (6.6%) were also commonly seen. The overall CFR was 7.8% (n=8) and all fatal cases (except 1 with unknown ethnicity) were in Indigenous peoples. The *emm* types of the fatal cases were all different.

Invasive *Haemophilus influenzae* disease (Hi)

Overall, there were no significant changes in the age-standardized annual incidence rates of *Haemophilus influenzae* type b (Hib) ($p = 0.18$) or Hi non-b ($p = 0.15$) from 2006 to 2013. Except for 6 cases with missing ethnicity and 1 non-Indigenous case, all the other 102 cases were First Nations and Inuit people. Of the 12 Hib cases, 10 were under 18 months of age; 4 had completed their primary vaccine series, 5 had received the vaccine but were not up-to-date and 1 was not vaccinated.

Figure 2 shows the serotype distribution of Hi cases. During the study period, Hi type a (Hia) accounted for 69.8% of the cases, followed by Hib (11.3%) and Hi non-typable (10.4%). No serotype e cases were reported. The annual incidence rate (per 100,000 population) of Hia increased significantly ($p = 0.004$) from 2006 to 2013. Fifty-three (71.6%) of Hia cases were in children under than 5 years. The incidence rate of Hia was the highest for infants less than 1 year (132.68, CI: 88.86–190.55), followed by children aged 1 to 4 years (28.31, CI: 18.14–42.12).

In total, 87.5% (n=91) of Hi cases were hospitalized. The most common manifestations (**Table 3**) were pneumonia (38.7%), septicemia/bacteremia (34.0%), meningitis (22.6%), and septic arthritis (10.4%). The overall CFR was 8.5% (n=8) and all fatal cases were of Hia.

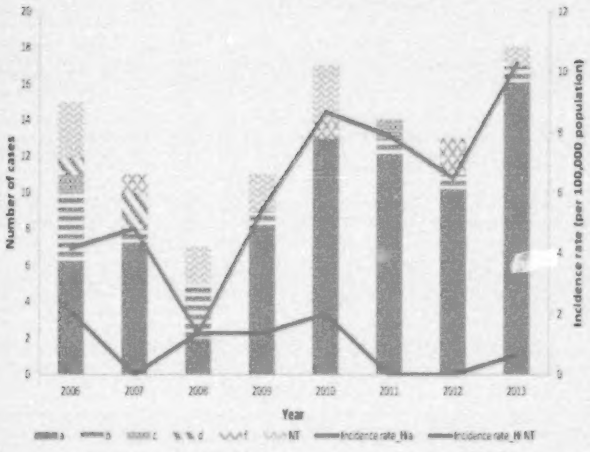
Invasive meningococcal disease (IMD)

Of 13 IMD cases, 8 were serogroup B (all under 5 years of age), 2 were C (both between 40 and 59 years) and 3 were W (all under 10 years of age). In terms of manifestation, 4 cases had meningitis only, 4 had meningitis with septicemia/bacteremia or other conditions, 2 had septicemia/bacteremia only (**Table 3**). Two cases died; both had serogroup B.

Invasive Group B streptococcal disease (GBS) of the newborn

Of 8 cases of GBS of the newborn, 6 were early onset and 2 were late onset. The serotyping information was available for only 3 cases, 1 serotype Ia and 2 serotype III. Septicemia/bacteremia was the most common manifestation

Figure 2: Serotype distribution of invasive *Haemophilus influenzae* disease cases and serotype specific incidence rates in Northern Canada, by year, 2006–2013[1]



Abbreviations: NT, non-typeable; Hia, *Haemophilus influenzae* type a; Hi NT, *Haemophilus influenzae* non-typeable
[1] Three cases with serotype missing were excluded

(n=6), followed by meningitis (n=2) and pneumonia (n=2) (**Table 3**). No deaths were reported.

Discussion

In Northern Canada, the incidence of IPD, iGAS and Hi was 2.6 to 10 times higher than in the rest of Canada, especially among First Nations and Inuit people. These findings are consistent with previous Canadian and international circumpolar studies (3-6,21-23).

IPD accounted for half of the IBDs cases during the study period and continues to be a substantial cause of morbidity in Northern Canada, especially for infants and people aged 60 years and greater. The risk of death did not vary between Indigenous and non-Indigenous peoples.

Routine PCV7 vaccination of infants started in 2002 in some Northern regions and IPD incidence has reduced since then (5,6). This report demonstrates a further reduction and sustained decreasing trend in PCV7 serotype-caused IPD as well as the total incidence of IPD. The incidence of IPD caused by PCV13 has not changed. More longitudinal data are needed for further assessment of PCV13. The efficacy and effectiveness of PPV23, which differs from conjugated vaccines, are relatively lower (24-26), and the protection of PPV23 appears to wane after 5 years (27). It is not surprising to see cases in individuals who had been immunized.

Routine Hib vaccine programs have been implemented in Canada since 1997 (8) and (Hib) is now rare in the country. However, it is still a concern in Northern Canada with a substantially higher rate among Indigenous infants. Some studies suggested that poor health, environmental and housing conditions of Indigenous children may be potential risk factors (28-31). Hia has been a predominant serotype in Northern Canada since the beginning of ICS (5,22,32), whereas non-typaeble Hi and type f are more common in other circumpolar regions (32). This report also demonstrates the significant increasing trend of Hia. National data of Hi non-b types are aggregated into a single category, so the serotype specific trends and distributions of Northern Canada and the rest of the country cannot be compared.

IMD is generally rare in Northern Canada as well as the rest of the country (33). Since the implementation of childhood immunization programs for MenC, the incidence of meningococcal C is at an all-time low and meningococcal B is the predominant serotype in Canada (33). None of the cases reported during the study period could have been prevented by the vaccine programs at the time.

The incidence of iGAS increased between 1999 and 2005 (5,32) but decreased between 2006 and 2013. This change in trend should be interpreted with caution due to the small number of cases. The most common *emm* types were *emm*1, *emm*59 and *emm*91, similar to the distribution reported between 1999 and 2005 (5) and the rest of Canada (34), but different than that of other circumpolar regions such as Alaska where *emm*3, *emm*41 and *emm*12 were more common (5,32).

Due to the lack of live birth population data and extremely small number of cases of GBS of the newborn, it is difficult to compare the disease epidemiology between Northern Canada and the rest of Canada or other countries.

It is important to consider the limitations when interpreting the data in this report. The disease characteristics, e.g., serotyping, outcomes and immunization history, could be underestimated or overestimated due to missing data. The analyses of GBS and IMD were limited due to the extremely small case numbers and the lack of live birth population data. Due to the instability of results based on the small number of cases and small population sizes, caution should be used when interpreting results. Finally, further detailed analysis of Inuit, First Nations and Métis individuals was not possible due to small numbers and the lack of availability of population estimates of these individual groups in the ICS region.

Compared to the rest of Canada, data indicate that Northern Canada has higher incidence rates of IPD, Hi and iGAS, especially among infants and seniors. First Nations and Inuit groups are more vulnerable to the diseases than non-Indigenous people. Enhanced national surveillance of IBDs is needed to better understand the disease disparities between Northern Canada and the rest of the country. In Canada, ICS is the only surveillance system that captures both epidemiological and laboratory data on IBDs for Northern populations. Ongoing surveillance will contribute to the understanding of disease epidemiology, which will ultimately assist in the formulation of prevention and control strategies, including immunization recommendations, for Northern populations.

Acknowledgements

We would like to thank all members of the Canadian International Circumpolar Surveillance Invasive Bacterial Diseases Working Group, particularly A. Mullen, B. Lefebvre, C. Cash, C. Foster, G. Tyrrell, H. Hannah, J. Proulx, K. Dehghani, Y. Jafari, for their invaluable contribution to the ICS surveillance and to this report. We would also like to thank J. Cunliff and M. St-Jean for database management and N. Abboud for project management.

Conflict of interest

None.

Funding

Funding for Canada's participation in International Circumpolar Surveillance was paid for by the Public Health Agency of Canada.

References

1. Parkinson AJ, Bruce MG, Zulz T. International Circumpolar Surveillance, an Arctic network for surveillance of infectious diseases. Emerg Infect Dis. 2008 Jan;14(1):18-24.
2. Vaudry W, Talling D. Invasive pneumococcal infection in first nations children in northern Alberta. Can Comm Dis Rep 2002;28:165-72.
3. Christiansen J, Paulsen P, Ladefoged K. Invasive pneumococcal disease in Greenland. Int J Circumpolar Health 2004;63 Suppl 2:214-218.
4. Singleton R, Hammitt L, Hennessy T, Bulkow L, DeByle C, Parkinson A, et al. The Alaska Haemophilus influenzae type b experience: lessons in controlling a vaccine-preventable disease. Pediatrics. 2006 Aug;118(2):e421-9.
5. Degani N, Navarro C, Deeks SL, Lovgren M. Invasive bacterial diseases in northern Canada. Emerg Infect Dis. 2008 Jan;14(1):34-40.
6. Bruce MG, Deeks SL, Zulz T, Navarro C, Palacios C, Case C, et al. Epidemiology of Haemophilus influenzae serotype a, North American Arctic, 2000-2005. Emerg Infect Dis. 2008 Jan;14(1):48-55.
7. National Advisory Committee on Immunization (NACI). Update on the invasive pneumococcal disease and recommended use of conjugate pneumococcal vaccines. Can Comm Dis Rep 2010; 36(ACS-3):1-30.
8. Public Health Agency of Canada. Canadian Immunization Guide. Ottawa (ON). http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php.
9. National Advisory Committee on Immunization (NACI). An update on the invasive meningococcal disease and meningococcal vaccine conjugate recommendations. An Advisory Committee Statement (ACS). Can Comm Dis Rep 2009; 36 (ACS-3):1-40.
10. Public Health Agency of Canada. Case definitions for communicable diseases under national surveillance. Can Comm Dis Rep 2009;35-Suppl 2:1-123.
11. Austrian R. The quellung reaction, a neglected microbiologic technique. Mt Sinai J Med. 1976 Nov-Dec;43(6):699-709.
12. Lovgren M, Spika JS, Talbot JA. Invasive Streptococcus pneumoniae infections: serotype distribution and antimicrobial resistance in Canada, 1992-1995. CMAJ. 1998 Feb 10;158(3):327-31.
13. Centers for Disease Control and Prevention. Streptococcus laboratory. Protocol for emm typing. Atlanta (GA): The Centers; 2015 Feb 26. http://www.cdc.gov/streplab/protocol-emm-type.html.
14. Falla TJ, Crook DW, Brophy LN, Maskell D, Kroll JS, Moxon ER. PCR for capsular typing of Haemophilus influenzae. J Clin Microbiol. 1994 Oct;32(10):2382-6.
15. Lau SK, Woo PC, Mok MY, Teng JL, Tam VK, Chan KK, et al. Characterization of Haemophilus segnis, an important cause of bacteremia, by 16S rRNA gene sequencing. J Clin Microbiol. 2004 Feb;42(2):877-80.
16. Riou JY, Guibourdenche M. Laboratory methods, Neisseria and Branhamella. Paris (FR): Institut Pasteur; 1992.
17. Tsang RS, Rudolph K, Lovgren M, Bekal S, Lefebvre B, Lambertsen L, et al. International circumpolar surveillance interlaboratory quality control program for serotyping Haemophilus influenzae and serogrouping Neisseria meningitidis, 2005 to 2009. J Clin Microbiol. 2012 March;50(3):651-6.
18. Statistics Canada, Demography Division, Demographic Estimates Section, July Population Estimates, 2011 Final Intercensal Estimate. Ottawa (ON): Statistics Canada; 2015.
19. Statistics Canada. Table105-0503 - Health indicator profile, age-standardized rate, annual estimates, by sex, Canada, provinces and territories, occasional, CANSIM (database). Ottawa (ON): Statistics Canada; 2015. http://www5.statcan.gc.ca/cansim/pick-choisir?lang=eng&p2=33&id=1050503#F57.
20. Fay MP, Feuer EJ. Confidence intervals for directly standardized rates: a method based on the gamma distribution. Stat Med. 1997 Apr 15;16(7):791-801.
21. Helferty M, Rotondo JL, Martin I, Desai S. The epidemiology of invasive pneumococcal disease in the Canadian North from 1999 to 2010. Int J Circumpolar Health. 2013 Aug 5;72. doi:10.3402/ijch.v72i0.21606.
22. Rotondo JL, Sherrard L, Helferty M, Tsang R, Desai S. The epidemiology of invasive disease due to Haemophilus influenzae serotype a in the Canadian North from 2000 to 2010. Int J Circumpolar Health. 2013 Aug 5;72. doi:10.3402/ijch.v72i0.21142.
23. Gounder PP, Zulz T, Desai S, Stenz F, Rudolph K, Tsang R, et al. Epidemiology of bacterial meningitis in the North American Arctic, 2000-2010. J Infect. 2015 Aug;71(2):179-87.

24. Melegaro A, Edmunds WJ. The 23-valent pneumococcal polysaccharide vaccine. Part I. Efficacy of PPV in the elderly: a comparison of meta-analyses. Eur J Epidemiol. 2004;19(4):353-63.
25. Huss A, Scott P, Stuck AE, Trotter C, Egger M. Efficacy of pneumococcal vaccination in adults: a meta-analysis. CMAJ. 2009 Jan 6;180(1):48-58.
26. Leventer-Roberts M, Feldman BS, Brufman I, Cohen-Stavi CJ, Hoshen M, Balicer RD. Effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive disease and hospital-treated pneumonia among people aged ³65 years: a retrospective case-control study. Clin Infect Dis. 2015 May 15;60(10):1472-80.
27. Andrews NJ, Waight PA, George RC, Slack MP, Miller E. Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. Vaccine. 2012 Nov 6;30(48):6802-8.
28. Banerji A, Bell A, Mills EL, McDonald J, Subbarao K, Stark G, et al. Lower respiratory tract infections in Inuit infants on Baffin Island. CMAJ. 2001 Jun 26;164(13):1847-50.
29. Koch A, Molbak K, Homoe P, Sorensen P, Hjuler T, Olesen ME, et al. Risk factors for acute respiratory tract infections in young Greenlandic children. Am J Epidemiol. 2003 Aug 15;158(4):374-84.
30. Kovesi T, Creery D, Gilbert NL, Dales R, Fugler D, Thompson B, et al. Indoor air quality risk factors for severe lower respiratory tract infections in Inuit infants in Baffin Region, Nunavut: a pilot study. Indoor Air. 2006 Aug;16(4):266-75.
31. Banerji A, Greenberg D, White LF, Macdonald WA, Saxton A, Thomas E, et al. Risk factors and viruses associated with hospitalization due to lower respiratory tract infections in Canadian Inuit children : a case-control study. Pediatr Infect Dis J. 2009 Aug;28(8):697-701.
32. Zulz T, Bruce MG, Parkinson AJ. International circumpolar surveillance. prevention and control of infectious diseases: 1999-2008. Circumpolar Health Suppl. 2009;4:13-30.
33. Li YA, Tsang R, Desai S, Deehan H. Enhanced surveillance of invasive meningococcal disease in Canada, 2006-2011. Can Comm Dis Rep 2014;40(9):160-9.
34. Public Health Agency of Canada, National Microbiology Laboratory. National Laboratory Surveillance of Streptococcal Diseases In Canada - Annual Summary 2013. 2014.

Evaluation of the enhanced Invasive Pneumococcal Disease Surveillance System (eIPDSS) pilot project

Wijayasri S[1,2], Li YA[2], Squires SG[2]*, Martin I[3], Demczuk W[3], Mukhi S[3]

Affiliations

[1]University of Saskatchewan, School of Public Health, Saskatoon, SK

[2]Infectious Diseases Prevention and Control Branch, Public Health Agency of Canada, Ottawa, ON

[3]National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, MB

***Correspondence:** susan.squires@phac-aspc.gc.ca

Abstract

Background: Invasive pneumococcal disease (IPD) causes significant morbidity in Canada, yet with routine surveillance, it is difficult to interpret current IPD trends in serotype distribution and antimicrobial resistance. The enhanced Invasive Pneumococcal Disease Surveillance System (eIPDSS) pilot project was designed to facilitate a better understanding of IPD trends at the national level by linking epidemiologic and laboratory (epi-lab) data.

Objectives: To evaluate the eIPDSS by assessing five attributes (usefulness, data quality, simplicity, acceptability and timeliness) and to develop recommendations for future national IPD surveillance.

Methods: An evaluation was developed that assessed the five key attributes through a qualitative survey sent to eight eIPDSS users as well as a quantitative analysis of the eIPDSS database. Recommendations were based on the results of both the survey and the analysis.

Results: The response rate to the survey was 100%. The majority of the survey respondents found the eIPDSS to be useful (75%), simple (100%) and acceptable (86%). Analysis of the eIPDSS database revealed that the majority of IPD cases (61%) were assessed as timely. Data quality and data management mechanisms were identified as issues by both survey respondents and the analysis of the database. Consultation with public health, regular audits and upgrades to the platform are recommended to address data quality and management issues.

Conclusion: The epi-lab linked data of the eIPDSS enables the detection and analysis of IPD serotype distribution and antimicrobial resistance trends. This web-based system facilitates data collection and is simple, acceptable and timely. With improvements that address data quality and management issues, it is feasible to develop a national surveillance system that links epi-lab data.

Suggested citation: *Wijayasri S, Li YA, Squires SG, Martin I, Demczuk W, Mukhi S. Evaluation of the enhanced Invasive Pneumococcal Disease Surveillance System (eIPDSS) pilot project. Can Comm Dis Rep 2016; 42:81-5.*

Introduction

Invasive pneumococcal disease (IPD) is an infectious disease caused by *Streptococcus pneumoniae*, which can cause severe morbidity and mortality, especially among young children and the elderly. Globally, an estimated 1.6 million people, including one million children less than five years of age, die of IPD annually (1). IPD has been nationally notifiable in Canada since 2000 (2) and is vaccine-preventable. Currently in Canada, a publicly funded pneumococcal conjugate 13 (PCV13) vaccine is available for infants and the pneumococcal polysaccharide vaccine (PPV23) is available to adults over the age of 65 and those considered at high risk for IPD (3).

There are currently 92 serotypes of *S. pneumoniae* recognized worldwide, 15 of which cause the majority of disease in Canada. Approximately 50 different serotypes are identified each year (4). The two vaccines cover the 24 most common serotypes (4). While Canada is experiencing a decrease in incidence of IPD that is reflective of an effective immunization program (5), the rising incidence of non-vaccine serotypes and antimicrobial resistan (AMR) serotypes are of particular concern.

Historically, epidemiologic and laboratory (epi-lab) linked data have not been available at the national level. The concept for the enhanced Invasive Pneumococcal Disease Surveillance System (eIPDSS) pilot project was devised to address shortcomings in the current routine surveillance methods, namely the inability to identify integrated epidemiologic and laboratory trends to provide evidence for vaccination programs and detect AMR serotype trends. The eIPDSS pilot project was launched in New Brunswick in April 2011 to allow for enhanced surveillance that would foster a better understanding of IPD trends,

especially changes in serotype distribution and antimicrobial resistance (AMR). This innovative project promoted collaborative working relationships between the provincial and the federal public health programs and allowed for the technological transformation and modernization of IPD surveillance.

The eIPDSS process and platform

This pilot was jointly managed by the National Microbiology Laboratory (NML) and the Centre for Immunization and Respiratory Infectious Diseases (CIRID) of the Public Health Agency of Canada, partners at the New Brunswick Ministry of Health and regional hospital laboratories and regional public health. The data collection process involved three points of entry – the local healthcare facilities, the NML, and regional and provincial public health offices. **Figure 1** presents the data process of the eIPDSS, from specimen collection to completion of the electronic record. The NML posted laboratory information on the different serotypes onto the eIPDSS platform, which the provincial epidemiologist linked to the epidemiological information, including vaccination history and risk factors using a unique identifier or through probabilistic matching. These data were then readily available for extraction by all federal- and provincial- level surveillance partners through the platform.

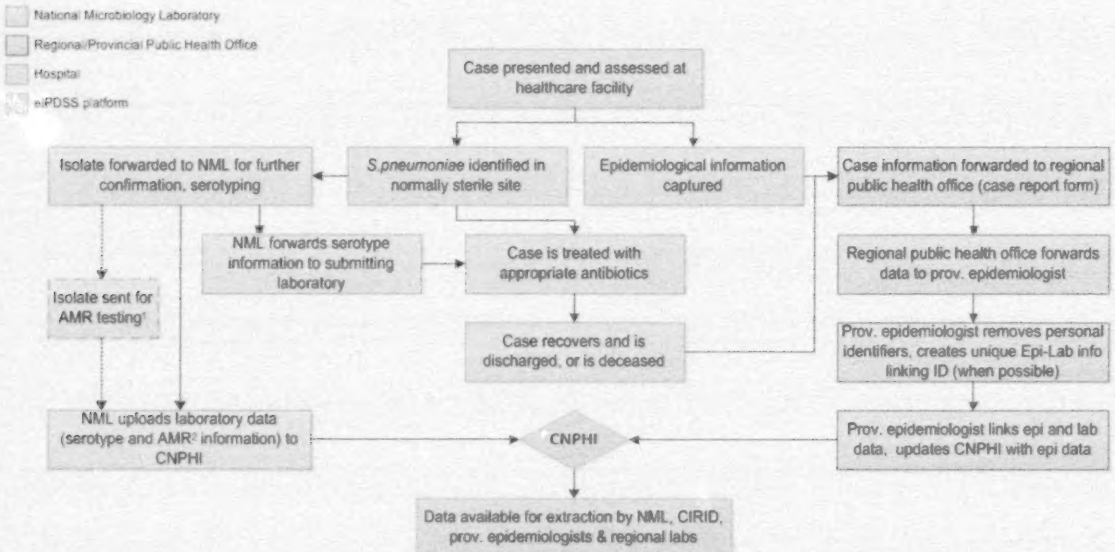
The Canadian Network for Public Health Intelligence's (CNPHI) Web Data technology was used to rapidly develop the pilot system platform. Although Web Data technology is not typically used for long-term surveillance systems, it was selected due to its ability to rapidly and interactively set up a database and the inherent flexibility required for the pilot phase (6).

The objective of this study was to evaluate the eIPDSS pilot project by assessing five surveillance attributes — usefulness, data quality (completeness and validity), simplicity, acceptability and timeliness — and provide recommendations to improve these attributes to inform the development of national integrated surveillance systems that link epi-lab data.

Methods

An evaluation framework was developed using guidelines outlined in Health Canada's *Framework and Tools for Evaluating Health Surveillance Systems* (7) and the *Updated Guidelines for Evaluating Public Health Surveillance* published by the Centers for Disease Control and Prevention (CDC) [8]. This framework was designed to assess five important attributes -- usefulness and data quality were selected to assess whether the eIPDSS is effective in collecting epi-lab linked data; simplicity, acceptability and timeliness were selected to assess the feasibility of

Figure 1: Data flow process of enhanced Invasive Pneumococcal Disease Surveillance System pilot project, 2011–2015


National Microbiology Laboratory
Regional/Provincial Public Health Office
Hospital
eIPDSS platform
Case presented and assessed at healthcare facility
Isolate forwarded to NML for further confirmation, serotyping
S.pneumoniae identified in normally sterile site
Epidemiological information captured
Case information forwarded to regional public health office (case report form)
NML forwards serotype information to submitting laboratory
Case is treated with appropriate antibiotics
Regional public health office forwards data to prov. epidemiologist
Isolate sent for AMR testing[1]
Case recovers and is discharged, or is deceased
Prov. epidemiologist removes personal identifiers, creates unique Epi-Lab info linking ID (when possible)
NML uploads laboratory data (serotype and AMR[2] information) to CNPHI
CNPHI
Prov. epidemiologist links epi and lab data, updates CNPHI with epi data
Data available for extraction by NML, CIRID, prov. epidemiologists & regional labs

Abbreviations: AMR, Antimicrobial resistance; CIRID, Centre for Immunization and Respiratory Infectious Diseases; CNPHI, Canadian Network of Public Health Intelligence; Epi, epidemiology; ID, Identifier; Lab, laboratory; Prov, Provincial; *S. pneumonia, Streptococcus pneumoniae*

[1]AMR is only tested on *S. pneumoniae* isolates sent to the National Microbiology Laboratory (NML) from select health regions in New Brunswick. AMR testing is done by the Health Sciences Centre (Winnipeg, Manitoba).
[2]If testing is performed.

developing a national IPD surveillance system that links epidemiologic and laboratory data.

These attributes were assessed through a combination of two approaches: 1) a qualitative, anonymous survey and 2) a detailed analysis of the pilot project's data flow process, database and operations. The survey was sent to eight primary eIPDSS users who used the system regularly (four provincial-level epidemiologists and surveillance analysts in New Brunswick and four federal-level epidemiologists at CIRID and laboratorians at the NML). The analysis was conducted by the authors.

The following outlines how each attribute was assessed:

Usefulness: A surveillance system is considered useful if it contributes to the prevention and control of adverse health related events (8). To assess the various "usefulness indicators" outlined by the CDC guidelines, the system's operations and objectives were reviewed and a quantitative analysis of the data was performed. Survey respondents also answered questions specific to how they use the system and its data, their opinions on the usefulness of the eIPDSS data, how the system could be made more appropriate to their needs and whether the pilot project was or could be made ready for national implementation.

Data quality: Data quality was assessed through three indicators: the application of a uniform national case definition (see box below), completeness of the data elements and validity of the captured cases. Completeness was assessed by calculating the percentage of missing values (both "unknown" and blank responses) of selected data elements. Validity was assessed by comparing the counts of IPD cases from New Brunswick captured in the Canadian Notifiable Disease Surveillance System (CNDSS) with data from the eIPDSS.

Case definition of invasive pneumococcal disease (9)

A confirmed case is when there is clinical evidence of invasive disease with laboratory confirmation of infection:

- Isolation of *Streptococcus pneumoniae* from a normally sterile site (excluding the middle ear and pleural cavity) OR
- Demonstration of *S. pneumoniae* DNA from a normally sterile site (excluding the middle ear and pleural cavity)

Abbreviation: DNA, deoxyribonucleic acid

Simplicity: This refers to the ease of data flow and management of the system (8) and was assessed through the stakeholder survey, using questions concerning ease of use, user opinions on features that facilitate or hinder simplicity and reliability of the system to collect, manage and access data properly without failure.

Acceptability: This refers to the willingness of surveillance staff to implement the system and users of the system to use the data generated (8). Acceptability was assessed through the stakeholder survey using questions related to features of the system that promoted or prevented acceptance.

Timeliness: Timeliness reflects the speed or delay between steps in a surveillance system (8). The number of days between the episode date and the date of report to the system was determined and examined for each case.

The recommendations were developed by the authors based on the results of the evaluation, including feedback from primary users.

Results and recommendations

Participation in the eIPDSS evaluation survey was 100%.

Usefulness

Six of the survey respondents (75%) felt that the eIPDSS data were useful. None of the data elements were identified as not useful. A quantitative analysis of the eIPDSS data also revealed that the eIPDSS was useful. The system was able to capture all confirmed cases of IPD—it detected epidemiologic and laboratory trends and was able to provide estimates of magnitude of IPD morbidity and mortality.

Recommendations to improve usefulness:

1. Discuss with surveillance partners the inclusion of the following elements to provide more detailed morbidity / mortality information:
    a. Intensive care unit admissions
    b. Outbreak indicator
    c. Date of death
2. Review the current data dictionary and case report form with surveillance partners to reflect necessary changes.

Data quality

Of the 273 cases with episode dates between April 4, 2011 and June 8, 2015, 98% (n=267) met the national case definition. Six cases were removed from the dataset because they did not meet the national case definition—two had pleural fluid isolates and four had pneumonia without an accompanying positive blood isolate.

Completeness of several data elements was below the pre-established satisfactory level of 90%, including clinical diagnosis (81%), length of hospital stay (88%), outcome (86%), underlying medical conditions (73%), Indigenous status (45%) and immunization history (71% to 73%). The use of a unique identifier for linking laboratory and epidemiologic dataset was considerably below the satisfactory level of completeness (34%) and follow-up with provincial surveillance partners revealed that obtaining a unique identifier to link laboratory and epidemiological data was problematic. However, 63% of the survey respondents found the data to be sufficiently complete, with AMR data collection and immunization history identified as areas that needed improvement.

Comparison between data from the CNDSS and eIPDSS found 100% agreement between case counts by each age group and sex, demonstrating that the eIPDSS data are valid.

Recommendations to improve data quality and completeness:

1. Consult with regional public health offices on ways to improve the collection of important data elements, especially clinical diagnosis and immunization history.
    a. Establish data quality indicators. A suggested indicator, currently used by the CDC, could be the proportion of reported cases with complete information, based on an established minimum dataset (10). This indicator could inform consultation with regional offices.
2. Include a "Record status" variable to distinguish confirmed cases from discarded cases.
3. A follow-up process should be developed, documented and agreed upon to maintain a high level of data quality and completeness and to improve responsiveness of the system. This follow-up process should include:
    a. An annual data audit.
    b. A mechanism to allow for changes in case information (e.g., changes to province of residence, errors, duplicates, etc.) that will be reflected on both laboratory and epidemiological sides.
    c. Agreed-upon delegation of follow-up responsibilities among elPDSS surveillance partners.
4. Should the provincial and national case definitions differ, ensure that the elPDSS is able to capture both provincial and national case definitions and filter cases accordingly. Consult with provincial public health to ensure that provincial case report forms include all data elements required for the assessment of the national case definition.

Simplicity

Seven respondents answered questions related to simplicity. All agreed that the current system was simple or very simple. However, respondents identified concerns due to difficulties with data uploading and extraction (possibly attributed to complexities with data management processes), as well as the use of probabilistic matching (matching variables such as age, sex and episode date) rather than the use of a unique identifier to link laboratory and epidemiologic datasets. These difficulties were identified as barriers to simplicity.

Recommendations to improve simplicity:

1. Migrate the elPDSS from Web Data technology to a more dedicated custom application on the CNPHI informatics platform that allows for:
    a. Automated epidemiologic and laboratory record linkage that enables easier data linking and eliminates the current practice of probabilistic matching.
    b. Extraction of data through filtering of elements.
    c. Summarized data reports and statistical analysis.
    d. Faster performance (uploading and extracting data).
2. Consult with regional public health offices to ensure NML laboratory numbers are recorded on the case report form and reported to the provincial ministry of health.

Acceptability

All eight respondents answered questions addressing acceptability. Seven (88%) indicated the system was acceptable or highly acceptable. Comments, however, identified difficulties. Editing of case information, data cleaning and assigning/removing duplicates were identified as barriers to acceptability at the provincial level. The security of the dataset was identified as a concern due to the lack of restriction of certain data elements (i.e., date of birth, geographical region). In addition, difficulties in collecting data from the regions were also a concern. Specifically, the collection of certain data elements, as well as restrictions to AMR testing in many of the regions, were identified as barriers to acceptability.

Recommendations to improve acceptability:

1. Review data-sharing mechanisms and discuss the restriction of certain variables to surveillance partners (e.g., date of birth, geolocator/postal codes).
2. Revisit and review AMR testing arrangements with regional public health offices.

Timeliness

The time between episode date and date of report ranged from six business days (from January to June 2015) to 18 days (from April to December 2011), with an average of 10 days for the entire pilot period. The majority of the cases (61%) were reported to the local public health office within seven business days of the episode date. Laboratory data were uploaded to the CNPHI Web Data technology on a weekly basis, while epidemiological information was updated quarterly. The elPDSS was deemed as timely.

Recommendations to improve timeliness:

None.

Considerations for national implementation

Seven of the eight survey respondents answered questions regarding the national implementation of elPDSS, of which six (75%) said that the pilot is or could be made ready for national implementation. Considering the simplicity, acceptability, usefulness and timeliness of the system, as well as the positive responses towards national expansion by the surveillance partners, the elPDSS could be expanded nationally after improvements are made based on the recommendations.

In addition, due to the similarities between IPD surveillance and surveillance of other invasive bacterial diseases (such as data elements and reporting mechanisms, and the flexibility of the pilot platform through CNPHI) the elPDSS could be adapted into an omnibus invasive bacterial disease surveillance system which would allow for robust and efficient surveillance of other invasive bacterial diseases, such as invasive meningococcal disease, invasive *Haemophilus influenzae* disease, invasive Group A streptococcal disease and invasive Group B streptococcal disease.

Conclusion

The evaluation of the eIPDSS pilot project has demonstrated that eIPDSS is a simple, timely, epi-lab linked surveillance system that captures representative, robust information for more accurate interpretations of IPD and antimicrobial susceptibility trends. Ultimately, the system could help to prevent IPD by giving explicit information on serotypes and vaccination status that would inform policy decisions and immunization and prevention programs.

The provincial/territorial surveillance partners have identified some concerns during the evaluation that could be addressed by implementing the recommendations to improve usefulness, data quality, simplicity and acceptability and expand the surveillance system to include four other nationally notifiable diseases. By leveraging the flexible CNPHI platform, continued consultation with eIPDSS surveillance partners and regular evaluations of the system, Canada could expand, streamline and modernize its national reporting mechanisms of invasive bacterial diseases.

Acknowledgements

This article would not have been possible without the involvement of all federal and provincial contributors. We would like to thank Louis-Alexandre Jalbert, Suzanne Savoie, Sophie Wertz and Rita Raafat Gad of the New Brunswick Ministry of Health for their expertise and input throughout the evaluation.

Conflict of interest

None.

Funding

This work was supported by the Public Health Agency of Canada.

References

1. European Centre for Disease Prevention and Control. Annual epidemiological report 2013. Stockholm: ECDC; 2013.
2. Public Health Agency of Canada. Nationally notifiable diseases. http://dsol-smed.phac-aspc.gc.ca/dsol-smed/ndis/list-eng.php.
3. Public Health `gency of Canada. Canadian Immunization Guide – Pneumococcal Vaccine. Ottawa ON: PHAC; 2016. http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-pneu-eng.php.
4. Public Health Agency of Canada. Invasive Pneumococcal disease for health professionals. Ottawa ON: PHAC; 2016. http://www.phac-aspc.gc.ca/im/vpd-mev/pneumococcal-pneumococcie/professionals-professionnels-eng.php.
5. Demczuk WHB, Martin I, Griffith A, Lefebvre B, McGeer A, Lovgren M, et al. Serotype distribution of invasive Streptococcus pneumoniae in Canada after the introduction of the 13-valent pneumococcal conjugate vaccine, 2010-2012. Can J Microbiol 2013 Dec; 59(12):778-788.
6. Mukhi SN, Chester TL, Klaver-Kibria JD, Nowicki DL, Whitlock ML, Mahmud SM, et al. Innovative technology for web-based data management during an outbreak. Online J Public Health Inform 2011 Jun; 3(1),1-13.
7. Health Surveillance Coordinating Committee, Health Canada. Framework and tools for evaluating health surveillance systems. Ottawa ON: Health Canada; 2004.
8. Centers for Disease Control and Prevention. Updated guidelines for evaluating public health surveillance systems: Recommendations from the guidelines working group. MMWR Recommendations and Reports 2001 July 27;50(RR-13);1-35.
9. Public Health Agency of Canada. Case definitions for communicable diseases under national surveillance. Can Comm Dis Rep 2009;35-Suppl 2: 34-35.
10. Roush SW. Chapter 18: Surveillance indicators. In: Roush SW, Baldy LM, eds. Manual for the surveillance of vaccine-preventable diseases. Atlanta: Centres for Disease Control and Prevention; 2012.

OUTBREAK REPORT

Outbreak of Shigella sonnei in Montréal's ultra-Orthodox Jewish community, 2015

Pilon PA[1,2*], Camara B[1], Bekal S[3,4]

Abstract

An outbreak of *Shigella sonnei* that occurred in the ultra-Orthodox Jewish community (UOJC) was the subject of an investigation and response by the Montréal Regional Public Health Department, who collaborated with several health and community partners. A total of 27 confirmed cases were reported in this outbreak, which lasted from February to June 2015. The epidemic curve was compatible with a point source with secondary person-to-person transmission. In 11 of the 27 cases, pulsed-field gel electrophoresis (PFGE) analysis of strains found a single PFGE pattern newly identified in Quebec. Almost all strains tested showed resistance to ampicillin and trimethoprim-sulfamethoxazole (TMP/SMX). All the cases resided in centre west Montréal. Most of the cases were under 5 years old and attended a daycare centre, an environment recognized to be conducive to the transmission of enteric diseases. The Montréal Regional Public Health Department sent timely information to families, daycare and school stakeholders, community partners and synagogues in the UOJC, which helped reduce the transmission of shigellosis in the community.

Affiliations

[1]Infectious Disease and Prevention Control, Montréal Regional Public Health Department, Montréal, QC

[2]School of Public Health, Université de Montréal, Montréal, QC

[3]Laboratoire de santé publique du Québec, Sainte-Anne-de-Bellevue, QC

[4]Department of Microbiology and Immunology, Université de Montréal, Montréal, QC

***Correspondence:** ppilon@santepub-mtl.qc.ca

Suggested citation: *Pilon PA, Camara B, Bekal S. Outbreak of Shigella sonnei in Montréal's ultra-Orthodox Jewish community, 2015. Can Comm Dis Rep 2016;42:86-90.*

Background

On March 25, 2015, the Montréal Regional Public Health Department detected a statistically significant space-time cluster of 7 cases of shigellosis reported in the previous 12 days using SaTScan™ analytical software. The first epidemiologic investigations indicated that 3 of the 7 cases were children from the ultra-Orthodox Jewish community (UOJC). The other 4 cases had contracted the infection while travelling, and there were no links between them. Prior to this cluster, on February 25, there had been a report of a case in a daycare centre in this community; this child's symptoms had begun on February 19. Based on epidemiologic and historical data, an outbreak of shigellosis in the Montréal UOJC was strongly suspected and an investigation was launched.

Meanwhile, in December 2014 (1), New York City issued a public health alert regarding an outbreak involving 43 cases of *Shigella sonnei* affecting two similar communities. Because members of the UOJC regularly travel between Montréal and New York, it was important to investigate a possible link between the two outbreaks. The objectives of this investigation were to further characterize the *S. sonnei* outbreak in the UOJC, develop hypotheses and guide the Montréal Regional Public Health Department's potential interventions. An investigation report was written to share intervention strategies and to serve as a reference document for similar investigations.

Methodology

Case definition

A case was defined as a Montréal resident belonging to the UOJC, with no history of recent travel abroad and with a laboratory confirmation of *S. sonnei* infection, reported to the Montréal Regional Public Health Department between January 1 and August 31, 2015.

Case finding and data collection

Cases were identified through Quebec's registry of notifiable diseases. Data were collected through the registry and then by examining case files from the epidemiologic survey. Cases were assigned to the UOJC or an orthodox group (e.g., Belz, Satmar, etc.) based on survey responses.

Laboratory Tests

Laboratory tests were performed in the medical microbiology laboratories of reporting hospitals (identification of genus and species and sensitivity profile). Identification was confirmed using pulsed-field gel electrophoresis (PFGE) at the Laboratoire de santé publique du Québec (LSPQ).

Epidemiologic analysis

A case list was generated and imported into Microsoft Excel 2010; the list included demographic, clinical and epidemiologic variables. Descriptive analyses were conducted using SPSS version 12.0.2.

Public health intervention

A survey was conducted with each family that had a reported case. Information on prevention was provided to the family and the appropriate daycare centre or school. Public health officials worked with two partners within the UOJC to inform community members through synagogues, daycare centres and schools and to strengthen hygiene practices.

Health system partners and the Laboratoire de santé publique du Québec were informed to increase vigilance among health professionals and enhance surveillance and to obtain confirmatory test results and characterization results from the laboratory.

Results

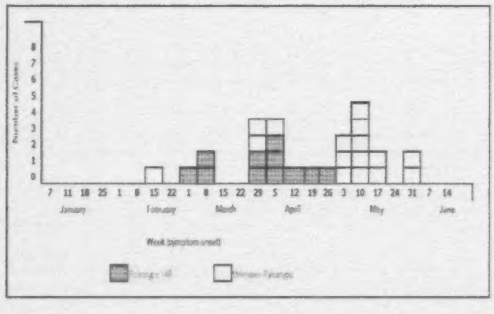
Case description based on time

Between February 19 and June 1, 2015, 27 confirmed cases of *S. sonnei* (contracted locally) occurred in the Montréal UOJC. This represented 79% (27/34) of all confirmed cases of *S. sonnei* reported in the area for the same period. The first case was observed on February 19, and the outbreak lasted five months. The peak occurred in May with 10 (about 37%) reported cases. This was followed by a decrease in June until there were no cases in July and August. Based on the 1- to 3-day incubation period, the case exposure period seems to have been between February 18 and May 28, 2015. The epidemic curve (**Figure 1**) was consistent with a point source with secondary person-to-person transmission.

Case description based on environment

All the cases resided in centre west Montréal. Of the 27 cases, 11 lived within the same postal code. The environments frequented by 23 of the 27 cases during their infectious period were known: 8 daycare facilities for 13 cases (57%), 3 primary schools for 5 cases (22%), their homes for 4 cases (17%) and a university for 1 case (4%). A daycare and a school had the highest incidence with 3 cases each.

Figure 1: Epidemic curve of the *Shigella sonnei* outbreak in the ultra-Orthodox Jewish community, Montréal area, February to June 2015[1]



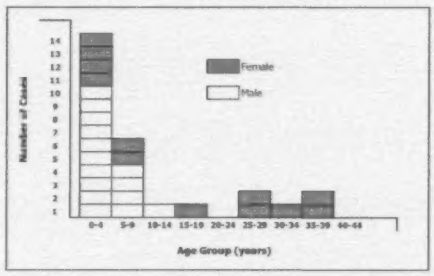
[1]The sampling date was used when the symptom onset date was missing (n=4 cases)

Description of case characteristics

Ages ranged from 1 to 35 years; the average age was 10 years, and the median age 4 years. Most (74%) of the cases were aged less than 10 years and 52% aged less than 5 years) [**Figure 2**].

There were 15 (56%) males and 12 (44%) females, a 1:3 M/F ratio. It is interesting to note that all the reported adult cases were women, probably because women are more involved in childcare.

Figure 2: Number of cases of the *Shigella sonnei* in the ultra-Orthodox Jewish community, by age group and sex, Montréal area, February to June 2015



Clinical presentation

Information on signs and symptoms was obtained for 22 of the 27 cases (**Table 1**). Fever and lower gastrointestinal symptoms were the most common symptoms. Fever and blood in the stool, indicating a more serious illness, occurred in 55% of the cases.

Table 1: Frequency of symptoms of *Shigella sonnei* in the ultra-Orthodox Jewish community, by age group (N=22)

Clinical presentation	0–9 years N=15 (%)	10–39 years N=7 (%)	All ages N=22 (%)
Diarrhea	15 (100)	7 (100)	22 (100)
Cramps / abdominal pain	14 (93)	5 (71)	19 (86)
Fever (≥38°C)	13 (86)	5 (71)	18 (82)
Blood in the stool	10 (67)	3 (43)	13 (59)
Unusual tiredness	9 (60)	3 (43)	12 (55)
Nausea	7 (47)	4 (57)	11 (50)
Vomiting	8 (53)	1 (14)	9 (41)

Abbreviation: N, number of cases

Medical consultation and hospitalization

The first contact with the health care system took place at an outpatient clinic for 24 cases (89%), and at a hospital emergency room for 3 cases (11%). Of the 24 cases who sought medical advice at a clinic, 18 (75%) reported to the same clinic, which appears to serve the UOJC.

None of the 27 cases had been hospitalized or had died at the time of the survey.

Treatment

Of the 25 cases who provided information on treatment, 17 (68%) received antibiotics; of these, 9 (53%) received ciprofloxacin. One case received ampicillin despite the strain's resistance profile (**Table 2**).

Table 2: Types of antibiotic used to treat *Shigella sonnei* infection in the ultra-Orthodox Jewish community (N=17)

Antibiotic treatment	Number (%)[1]
Ciprofloxacin	9 (53)
Azithromycin	2 (12)
Cefixime	2 (12)
Cephalexin	1 (6)
Ampicillin	1 (6)
Unknown	2 (12)
Total	17 (100)

[1] Adds up to more than 100% due to rounding

Laboratory results

All cases were laboratory confirmed by stool culture. Antibiotic sensitivity test results were available for 24 of the 27 cases; all were resistant to ampicillin and trimethoprim-sulfamethoxazole (TMP/SMX) [**Table 3**]. In all but 2 cases (1 ciprofloxacin and 1 cefixime), we had no data on sensitivity to these antibiotics or to azithromycin. The PFGE was performed in 11 of 27 cases, and a single genetic profile, pulsotype 148, was highlighted. This pulsotype, not previously identified in Quebec, was different from the PFGE pattern of the strain that caused an outbreak in the New York area in December 2014.

Table 3: Resistance profile of strains of *Shigella sonnei* based on antibiotic sensitivity testing (N=24)

Resistance profile	Number (%)
Ampicillin (R) + TMP/SMX (R)	16 (67)
Ampicillin (R) + TMP/SMX (I)	6 (25)
Ampicillin (R)	1 (4)
TMP/SMX (I)	1 (4)
Total	24 (100)

Abbreviations: R, Resistant; I, Intermediate

Potential sources of exposure

Of the 27 cases, 5 had a family relationship with another confirmed case already reported to the Montréal Regional Public Health Department. Of the 27 cases, 8 reported having had contact with a case with diarrhea before the start of their illness (including 3 contacts of confirmed cases). In 4 cases, the contact was with a family member, and for the 4 other cases, the only contact was via a daycare centre or primary school. The index case was a 2-year-old boy who attended a daycare centre (name not indicated), and whose symptoms began in February. Three members of his family also had diarrhea (unknown time sequence), but neither he nor anyone in his family had travelled recently. The 5 cases that followed in March (4 of which had identical pulsotypes) were also children aged between 4 and 10 years attending primary schools or different daycare centres, but did not seem to have any clear link to the index case. However, they were all of a similar age and could have participated in a common activity within the UOJC, giving rise to transmission. Of the cases that occurred in April and June, some were siblings of earlier cases and were probably infected through intrafamily transmission. One transmission may have also occurred in two daycare centres (DCC A and DCC B) and a primary school (primary school A) [initial case followed by other cases soon after] (**Table 4**).

Table 4: Distribution of confirmed cases of *Shigella sonnei* by exposure site (N=27)

Exposure site	Name of site	Number of cases
Daycare centre (N=13)	DCC A	3
	DCC B	2
	DCC C (girls)	1
	DCC D (boys)	1
	DCC E	1
	DCC F	1
	Daycare G (girls)	1
	Daycare H	1
	Unknown	2
Primary school (N=5)	A (boys)	3
	B (girls)	1
	C (girls)	1
University (N=1)	A	1
Other (N=8)	Residence	4
	Unknown	4

Abbreviation: DCC, daycare centre

Public health intervention

In this investigation, there was a response to each reported case of shigellosis confirmed by the laboratory. The response involved waiting at least 48 hours after cessation of diarrhea before sending the child back to daycare or school. In addition, an information sheet on the prevention of shigellosis was sent to the parents of affected children as well as the schools and daycares to increase the vigilance of other parents and officials in the various settings and to strengthen preventive measures.

Discussion

Shigellosis outbreaks are cyclical within the UOJC in Montréal, having occurred at different intensities at approximately 1- to 5-year intervals (**Table 5**) [2-9]. The regular recurrence of shigellosis in the UOJC is caused by the spread of the infectious agent as a result of travel to other similar communities with high prevalence of the disease or through chronic carriers who serve as a reservoir (2,5,10). The periodicity of Shigella outbreaks in the UOJC may be due to persistent low endemicity that generates an outbreak when a new cohort of young children with no previous shigellosis enters daycare or school (3).

Table 5: History of *Shigella sonnei* outbreaks in the ultra-Orthodox Jewish Community in the Montréal area, 1994 to 2015

Period	Number of confirmed cases
February and June 2015	27 (pulsotype 148)
August 2011 to December 2012 (8)	38 (several pulsotypes)
November 2007 to January 2008 (7)	11 (pulsotype 35 and related pulsotypes)
October 2004 to July 2005 (6,7)	76
July 1997 and January 1998 (6,7)	100
1994 to 1996 (2)	34 (pulsotypes 3, 3A)

The spread of shigellosis in this outbreak was caused by intrafamily transmission (4 of the 27 confirmed cases were siblings and several other cases had contact with family members suffering from diarrhea) and transmission at daycare centres (13 of the 27 cases) and school (5 of the 27 cases were connected to a primary school). Having close contacts, attending daycare, and having several young children at home were considered risk factors in previously reported outbreaks (3,5). The space-time cluster of cases and diversity of environments suggested person-to-person transmission. The fact that cases occurred in several groups within the UOJC supported the argument that community environments (in addition to the family environment) played a role in transmission. The characteristics of the Montréal outbreak were similar to those described in other cities (2–5). Undeveloped hygiene habits in young children and the low infectious dose required to transmit *S. sonnei* diminish the effectiveness of preventive measures in this population (3).

In the wake of outbreaks in recent years in Montréal, efforts had been made to try to reach different groups within the UOJC to prevent transmission of infectious diseases and, in particular, transmission of enteric diseases. As a result of these efforts, close ties were established with two Jewish community organizations who deal with various groups in Montréal's UOJC. Through them, preventive messages from the Montréal Regional Public Health Department were sent to those groups who have limited contact with anyone outside their community.

As soon as the outbreak was suspected, these two Jewish community organizations were notified and provided with the relevant information. The first organization has a medical clinic, a Yiddish telephone information line available to over 2,000 Jewish families, especially ultra-Orthodox groups, and contact with the synagogues; the second organization had counsellors in the community (daycare centre and schools). Both organizations participated in the Montréal Regional Public Health Department's effort to provide timely information on the unfolding shigellosis outbreak and the steps to prevent and control the transmission of this disease. Posters in French, English and Yiddish on handwashing were sent to families, daycare centres, schools and community partners in the UOJC to educate children and their parents and people working at daycare centres and schools. We assume that this timely information on preventive measures could help reduce the transmission of shigellosis. While the outbreak appeared to persist after March 25, preventive messages sent to the UOJC reduced the extent of the outbreak.

The decrease in the number of cases in the epidemic curve between April 5 and May 3 could be related to Passover celebration that took place from April 3 to 11. The closing of daycare centres and schools during this period reduced transmission.

Strains of *S. sonnei* from confirmed cases showed resistance to the first-line antimicrobials, ampicillin and TMP/SMX, which was considered a serious threat in the United States by the Centers for Disease Control and Prevention (11). This led clinicians to make more extensive use of antimicrobials such as ciprofloxacin or azithromycin, although some infections were already reported to be resistant to both these antibiotics.

The PFGE pattern of strain isolated in this investigation (pulsotype 148) showed that it had been previously unreported in Quebec and different from the strain responsible for the New York outbreak. Since strains of Shigella do not undergo routine laboratory monitoring, the possibility that this strain has been circulating for some time in Montréal or in other areas cannot be ruled out. Laboratory monitoring of Shigella strains could certainly facilitate epidemiologic surveillance in certain risk groups.

This investigation has several limitations. Only cases confirmed by laboratory analysis are identified in this report. The information collected during case finding suggests that the number of reported cases is lower than the true number of cases. Some cases of diarrhea that occurred in several families may have not been confirmed or reported to the Montréal Regional Public Health Department. Although intrafamily and community transmission in daycare centres and schools is strongly suspected, the probable source of exposure was unknown for a number of cases at the time of the survey.

Conclusion

This investigation describes an outbreak of *S. sonnei* in Montréal's UOJC that mainly affected preschool- and school-aged children. Identifying person-to-person transmission in a community that has limited contact with outsiders highlights the importance of maintaining and consolidating ties with UOJC partners to prevent outbreaks and respond quickly if they do occur. With these partners, it is possible to work with adults (parents, educators and teachers) to promote and strengthen preventive measures demonstrated to be effective in the prevention and control of infectious disease and, in particular, *Shigella* outbreaks (e.g. supervising children while they wash

their hands, decontaminating toys or other shared objects, temporarily keeping children with diarrhea out of daycare centres and schools).

Acknowledgements

We would like to thank all the investigators who worked on the cases and dealt with families and communities; the managers and stakeholders from the two Jewish community organizations for their work with the UOJC; Dr. Sandra Palmieri, Dr. Robert Allard, Maryse Lapierre and Dr. Carole Morissette for their comments.

Conflict of interest

None.

References

1. New York City Department of Health and Mental Hygiene. 2014 Alert #39: Outbreak of shigellosis in Borough Park and Williamsburg, December 17, 2014; [2 p.]. https://a816-health29ssl.nyc.gov/sites/NYCHAN/Lists/AlertUpdateAdvisoryDocuments/HAN_Shigella.pdf.
2. Sobel J, Cameron DN, Ismail J, Strockbine N, Williams M, Diaz PS, et al. A prolonged outbreak of *Shigella sonnei* infections in traditionally observant Jewish communities in North America caused by a molecularly distinct bacterial subtype. J Infect Dis. 1998 May;177:1405-9.
3. Garrett V, Bornschlegel K, Lange D, Reddy V, Kornstein L, Kornblum J, et al. A recurring outbreak of *Shigella sonnei* among traditionally observant Jewish children in New York City: the risks of daycare and household transmission. Epidemiol Infect. 2006;134:1231-6.
4. Daudens E, Dejour-Salamanca D, Isnard H, Mariani-Kurkdjian P, Filliol I, Bingen E. Épidémie de gastro-entérites aiguës à *Shigella sonnei* résistantes à l'amoxicilline, au cotrimoxazole et à l'azithromycine en Île-de-France – Janvier - Avril 2007. Saint-Maurice (FR): Institut de veille sanitaire; 2009 Dec. 18 p. (Available in French only: www.invs.sante.fr).
5. De Schrijver K, Bertrand S, Gutierrez Garitano I, Van den Branden D, Van Schaeren J. Outbreak of *Shigella sonnei* infections in the Orthodox Jewish community of Antwerp, Belgium, April to August 2008. Euro Surveill. 2011;16:pii=19838.
6. Andermann A. Shigellosis in the Montreal Jewish community: review of cases and recommended control measures. Montréal (QC): Direction de santé publique, Région de Montréal; 2005. 35 p.
7. Hannah H. Bilan des éclosions d'infections à *Shigella sonnei*, Montréal et au Québec, 5 août 2007 au 26 janvier 2008. Montréal (QC): Direction de santé publique, Région de Montréal; 2008. 21 p (Available in French only : http://www.santecom.qc.ca/bibliothequevirtuelle/hyperion/9782894946985.pdf).
8. Gardhouse C. Shigellose dans la communauté juive orthodoxe, Montréal, août 2011 – décembre 2012. Montréal (QC): Direction de santé publique, Région de Montréal; 2013. 31 p.
9. Susser S. Recurrent shigellosis outbreaks in the Montreal Jewish community: case study in health inequality. Montréal (QC): Direction de santé publique, Région de Montréal; 2012. 35 p.
10. Calderon-Margalit R, Navon-Venezia S, Gefen D, Amitai Z, Barda R, Vulikh I, Sompolinsky D. Biennial hyperepidemic shigellosis in an observant Jewish community. Epidemiol Infect. 2010;138:244-52. http://www.ncbi.nlm.nih.gov/pubmed/?term=Sompolinsky%20D%5BAuthor%5D&cauthor=true&cauthor_uid=19602299.
11. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. Atlanta (GA): CDC; 113 p. http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf.

Interim recommendations for the reporting of extensively drug resistant and pan-drug resistant isolates of Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter spp. and Stenotrophomonas maltophilia

German GJ[1], Jamieson FB[2], Gilmour M[3], Almohri H[4], Bullard J[5], Domingo MC[6], Fuller J[7], Girouard G[8], Haldane D[9], Hoang L[10], Levett PN[11], Longtin J[6], Melano R[2], Needle R[12], Patel SN[2], Rebbapragada A[13], Reyes RC[14], and Mulvey MR[3*]

Note

The recommendations in this publication should be considered preliminary for one year from the publication date. Comments regarding the document should be sent to Dr. Michael Mulvey. All comments received will be reviewed by the Canadian Public Health Laboratory Network Antimicrobial Resistance Subcommittee before the final recommendations are drafted and released.

Suggested citation: *German GJ, Jamieson FB, Gilmour M, Almohri H, Bullard J, Domingo MC, Fuller J, Girouard G, Haldane D, Hoang L, Levett PN, Longtin J, Melano R, Needle R, Patel SN, Rebbapragada A, Reyes RC, and Mulvey MR. Interim Recommendations for the Reporting of Extensively Drug Resistant and Pan Drug Resistant Isolates of Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter spp. and Stenotrophomonas maltophilia. Can Comm Dis Rep 2016;42:91-7.*

Affiliations

[1]Health PEI, Charlottetown, PEI

[2]Public Health Ontario Laboratories, Toronto, ON

[3]National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, MB

[4]LifeLabs, Toronto, ON

[5]Cadham Provincial Laboratory, Winnipeg, MB

[6]Laboratoire de santé publique du Québec, INSPQ, Ste-Anne-de-Bellevue, QC

[7]Alberta Provincial Laboratory for Public Health, Edmonton, AB

[8]Centre hospitalier universitaire Dr-Georges-L.-Dumont, Moncton, NB

[9]Queen Elizabeth II Health Science Centre, Halifax, NS

[10]BC Centre for Disease Control Public Health Laboratory, Vancouver, BC

[11]Saskatchewan Disease Control Laboratory, Regina, SK

[12]Newfoundland Public Health Laboratory, St. John's, NL

[13]Dynacare, Brampton, ON

[14]LifeLabs, Burnaby, BC

***Correspondence:** Michael.Mulvey@phac-aspc.gc.ca

1.0 Introduction

These recommendations are produced under the auspices and authority of the Canadian Public Health Laboratory Network, Antimicrobial Resistance Working Group. They represent a consensus of peer reviewed information and expert opinion on the most appropriate ways to test for and report a multi-drug resistant phenotype in common Gram-negative pathogens. These recommendations were developed for use by all Canadian non-veterinary clinical microbiology laboratories to provide standardization for provincial and national surveillance programs.

2.0 Background

Antimicrobial resistance is a growing concern for human health as bacterial pathogens continue to accumulate genes and genomic alterations that confer resistance to antimicrobials. Most concerning is the occurrence of multiple resistance traits within individual key pathogens, which greatly limits, if not entirely eliminates the arsenal of effective treatment options for those infections, thereby leading to poor clinical outcomes. In Canada, we have observed these highly resistant strains in *Enterobacteriaceae, Acinetobacter* spp., *Stenotrophomonas*

maltophilia, and *Pseudomonas aeruginosa* (1-3). There is a need for laboratories to classify organisms that are resistant to multiple antimicrobials in order to consistently and accurately share the information locally, nationally, and internationally with the medical community, public health authorities and policy makers. More specifically, classification as 'multi-drug resistant' is commonly an actionable finding within hospital Infection Prevention & Control programs. Recently, there has been a proposal to internationally standardize these definitions in selected Gram-positive and Gram-negative organisms (4), yet this proposal for interim definitions has not yet led to a revised definition or national recommendations.

The goal of this document is to provide Canadian laboratories with a framework for consistent reporting and monitoring of multi-drug resistant organisms (MDRO), extensively drug resistant organisms (XDRO), and pan-drug resistant organisms (PDRO). The recommendations were based on an interim international proposal published in 2012 for Gram-negative organisms (4). This document modifies the following for the Canadian setting: 1) Resistance was used instead of non-susceptibility (Intermediate and Resistant) to better match which antimicrobials will be clinically used for treating resistant infections; antimicrobials that are more easily tested in the laboratory; and those that would limit unnecessary reference testing. 2) MDRO rules are separated for commonly used antimicrobials in the community setting for urine infections and non-urine infections. 3) Rather than all classes of antimicrobials being considered in the definitions, only relevant classes that are commonly tested in Canadian clinical laboratories were considered. Also within a class of antimicrobials, resistance to the most commonly used antimicrobial for treating severe infections (i.e. meropenem or imipenem) was considered rather than an inferior drug for infections (i.e. ertapenem for the carbapenems). 4) Since XDRO definitions will fluctuate from country to country based on 2nd and 3rd line available antimicrobials, adjustments were made for antimicrobials available/approved for use in Canada rather than all drug categories listed in the Clinical Laboratory Standards Institute (CLSI) (5). The justification for these modifications can be found in **Appendix 1**. Over time as new antimicrobials become available, previously available antimicrobials lose effectiveness, or no longer available, the definitions will necessitate periodic review. The recommendations stated herein are considered interim and are open for stakeholder consultation such that future recommendations evolve to accommodate public health, community care, and acute care partners.

3.0 Recommendations for Antimicrobial Susceptibility Testing

3.1 A resistant interpretation of an isolate can be determined using disk diffusion, broth microdilution, or agar dilution following CLSI guidelines for the testing of Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter spp. and Stenotrophomonas maltophilia (5). A Health Canada or Federal Drug Administration (FDA) approved automated method or gradient diffusion strips can also be used for the generation of the antimicrobial susceptibility data.

3.2 Current CLSI breakpoints (M100) for resistance should be used when determining the designations of MDRO, XDRO, and PDRO. It is understood that some laboratories use automated methods with Food and Drug Administration (FDA; www.fda.gov) breakpoints that may differ from the CLSI recommendations. A laboratory using FDA breakpoints should include the breakpoint difference in any report for MDRO, XDRO, and PDRO.

3.3 Certain species of *Enterobacteriaceae* should not be tested for particular antimicrobial agents because of intrinsic resistance to the agent (**Table 1**, Exceptions).

4.0 Definitions of Screening/Testing for MDRO, XDRO and PDRO

These interim recommendations are to be applied only to clinical/diagnostic specimens. However, acute care and long term care facilities, and by extension health authorities, may choose to still apply the definitions of MDRO/XDRO/PDRO for screening purposes as determined by their own fiscal situation and local health resources. If isolates are part of a specialized surveillance program (e.g. in-patient screening), it should be clearly indicated in the laboratory report that the MDRO/XDRO/PDRO is pertinent for colonization or carriage status only.

4.1 *Enterobacteriaceae* Multi-Drug Resistance Definition

It is recognized that laboratories may not test Gram-negative isolates for all classes of antimicrobial agents and therefore would not be able to determine MDRO, XDRO, and PDRO. Therefore, we have included a category of multi-drug resistant organisms (MDRO) that should be considered for screening isolates for XDRO or PDRO.

4.1.1 There are four rules for MDRO status in *Enterobacteriaceae* which takes into consideration the specific specimen type (**Table 1**).

4.2 *Acinetobacter* spp. or *Pseudomonas aeruginosa* Multi-drug Resistance Definition

4.2.1 An isolate should be considered MDRO if resistant to **THREE** of the **FIVE** antimicrobial agents listed below (**Table 2**):

1. Ciprofloxacin
2. Piperacillin-tazobactam **OR** piperacillin (specifically for *P. aeruginosa*)
3. Ceftazidime **OR** cefepime
4. Imipenem **OR** meropenem
5. Tobramycin

4.3 *Stenotrophomonas maltophilia* Multi-Drug Resistance Definition

4.3.1 *S. maltophilia* is intrinsically resistant to all carbapenems and most cephalosporins. A clinical isolate should be considered an MDRO if it is resistant to trimethoprim-sulfamethoxazole and subsequent susceptibility testing indicates it is also resistant to an oral anti-microbial (minocycline or levofloxacin) [**Table 2**].

Table 1: Rules for the determination of Multi-Drug-, Extensively Drug-, Pan-Drug Resistant Organisms in *Enterobacteriaceae* from clinical isolates[a]

Rule	Speciman	Antimicrobial Groups	Interpretation
1	Urine	Cefixime OR Amoxicillin-clavulanate	**Resistance to THREE** of the **FOUR** groups = MDRO
		Ciprofloxacin	
		Trimethoprim-Sulfamethoxazole	
		Nitrofurantoin	
2	Non-Urine	(Cefixime OR Amoxicillin-clavulanate)	**Resistance to THREE of the THREE** groups = MDRO
		Ciprofloxacin	
		Trimethoprim-sulfamethoxazole	
3	All	Meropenem[b] AND (Ciprofloxacin OR Trimethoprim-sulfamethoxazole)	Resistance to a very broad spectrum antimicrobial and resistance to one of two commonly used and unrelated drug classes = MDRO
4	All	Tobramycin AND Gentamicin AND Piperacillin-Tazobactam AND (Ciprofloxacin OR Trimethoprim-sulfamethoxazole)	Resistance to two commonly susceptible drug classes and resistance to one of two commonly used and unrelated drug classes = MDRO
5	All	Tobramycin **AND** Gentamicin	Resistance to FOUR of the SIX antimicrobial groups = XDRO
		Piperacillin-Tazobactam	
		Imipenem **OR** Meropenem	
		Cefepime **OR** (cefotaxime/ ceftriaxone) **AND** ceftazidime	
		Ciprofloxacin	
		Trimethoprim-Sulfamethoxazole	
6	All	Same groups listed in rule #5	Resistance to SIX of SIX antimicrobial groups = PDRO

Abbreviations: MDRO, multi-drug resistant organisms; XDRO, extensively drug resistant organisms; PDRO, pan-drug resistant organisms

[a] Expert rules modified from Leclercq et al., 2013 (7)

[b] Imipenem can be substituted for meropenem with the exception of *Proteus* spp.

5.0 Confirmation of XDRO

5.1 *Enterobacteriaceae* XDRO Definition

5.1.1 An isolate that has been determined to be an MDRO should be considered an XDRO by testing/assessing resistance to other antimicrobial agents listed in this section.

5.1.2 Unlike the definition of MDRO for *Enterobacteriaceae*, the type of specimen does not need to be considered for the definition of XDRO.

5.1.3 An isolate of *Enterobacteriaceae* should be considered an XDRO when the isolate is resistant to **FOUR** of the **SIX** antimicrobial agents listed below (**Table 1**):

1. Tobramycin **AND** gentamicin
2. Piperacillin-tazobactam
3. Imipenem **OR** meropenem
4. Cefepime **OR** (cefotaxime/ceftriaxone) **AND** ceftazidime
5. Ciprofloxacin
6. Trimethoprim-sulfamethoxazole

5.2 *Pseudomonas aeruginosa* XDRO Definition

5.2.1 A *P. aeruginosa* should be considered an XDRO when the isolate is resistant to **FOUR** of the **SIX** antimicrobial agents listed below (**Table 2**):

1. Tobramycin
2. Piperacillin **OR** piperacillin-tazobactam
3. Imipenem **OR** meropenem **OR** doripenem
4. Cefepime **OR** ceftazidime
5. Ciprofloxacin
6. Colistin

5.2.2 A *P. aeruginosa* should be considered a PDRO when the isolate is resistant to **ALL** of the antimicrobial agents listed in 5.2.1.

5.3 *Acinetobacter* spp. XDRO Definition

5.3.1 An *Acinetobacter* spp. should be considered an XDRO when the isolate is resistant to **SIX** of the **EIGHT** antimicrobial agents listed below (**Table 2**):

1. Gentamicin **OR** Tobramycin
2. Piperacillin-tazobactam
3. Imipenem **OR** meropenem **OR** doripenem
4. Cefepime **OR** ceftazidime
5. Ciprofloxacin
6. Colistin
7. Doxycycline **OR** minocycline
8. Trimethoprim-sulfamethoxazole (note: intrinsically resistant to trimethoprim)

5.4 *Stenotrophomonas maltophilia* XDRO Definition

A *S. maltophilia* should be considered an XDRO if resistant to three oral antimicrobials (trimethoprim-sulfamethoxazole, minocycline, and levofloxacin). The isolate should be referred for complete antimicrobial susceptibility testing to exclude a PDRO (see **Table 2**).

6.0 Confirmation of PDRO

An *Enterobacteriaceae*, *P. aeruginosa*, *Acinetobacter* spp. should be considered a PDRO when the isolate is resistant to **ALL** antimicrobial agents listed in **Table 1** (rule 6), section 5.2.1, or 5.3.1, respectively. *S. maltophilia* should be considered a PDRO if it is resistant to all of the following: trimethoprim-sulfamethoxazole, levofloxacin, ceftazidime, and chloramphenicol.

7.0 Reporting to Reference Laboratories

7.1 Any laboratory identifying a MDRO that cannot confirm an XDRO or PDRO using additional antimicrobial susceptibility tests should send the isolate to a reference (provincial) laboratory (See **Appendix 2**).

7.2 The reference (provincial) laboratory should be notified of any XDR or PDR organisms identified and the isolate should be forwarded to the reference laboratory, and should include the following information:

1. Age of patient
2. Gender of patient
3. Type of clinical specimen (blood, respiratory, skin/soft tissue, or urine)
4. Date of collection
5. Antimicrobial susceptibility testing results from submitting laboratory
6. Out of Canada travel history in the last 3 months. Travel history is dated from the time of the first isolation of the organism. This is highly recommended for inpatients and desirable for outpatients. All countries traveled should be listed.

7.3 If multiple clinical isolates of the same species and susceptibility pattern are recovered from the same patient, send the isolate from the most invasive site where possible. Additional isolates of the same species and susceptibility pattern should be reported/sent to a reference laboratory no more frequently than every 7 days after the first isolate. Annotating as an MDRO/XDRO/PDRO on the clinical report should continue for each isolate regardless number of isolates or time interval between specimens.

Table 2: Definitions for the determination of Multi-Drug-, Extensively Drug-, Pan-Drug Resistant Organisms in select organisms

MDRO		XDRO / PDRO	
Definition	Antimicrobial Groups	Definitions	Antimicrobial Groups
Organism: *Pseudomonas aeruginosa*			
Resistance to **THREE** of the **FIVE** antimicrobial groups	Ciprofloxacin	Resistance to **FOUR** of the **SIX** antimicrobial groups = XDRO Resistance to **SIX** of the **SIX** antimicrobial groups = PDRO	Tobramycin
	Piperacillin-tazobactam **OR** piperacillin		Piperacillin-tazobactam **OR** piperacillin
	Ceftazidime **OR** cefepime		Imipenem **OR** meropenem **OR** doripenem
	Imipenem **OR** meropenem		Cefepime **OR** ceftazidime
	Tobramycin		Ciprofloxacin
			Colistin
Organism: *Acinetobacter* spp.			
Resistance to **THREE** of the **FIVE** antimicrobial groups	Ciprofloxacin	Resistance to **SIX** of the **EIGHT** antimicrobial groups = XDRO Resistance to all groups = PDRO	Gentamicin **OR** tobramycin
	Piperacillin-tazobactam		Piperacillin-tazobactam
	Ceftazidime **OR** cefepime		Imipenem **OR** meropenem **OR** doripenem
	Imipenem **OR** meropenem		Cefepime **OR** ceftazidime
	Tobramycin		Ciprofloxacin
			Colistin
			Doxycycline **OR** minocycline
			Trimethoprim-sulfamethoxazole
Organism: *Stenotrophomonas maltophilia*			
Resistance to **BOTH** antimicrobial groups	Trimethoprim-sulfamethoxazole Minocycline **OR** levofloxacin	Resistance to the **FIRST THREE antimicrobial groups = XDRO** **Resistance to all** antimicrobial groups = PDRO	Trimethoprim-sulfamethoxazole
			Minocycline
			Levofloxacin
			Ceftazidime
			Chloramphenicol

Abbreviations: MRDO, multi-drug resistant organsims; XDRO, extensively drug resistant organisms; PDRO, pan-drug resistant organisms

7.4 It is suggested that reports of clinical specimens found to contain XDRO or PDRO isolates incorporate the term Extensively Drug Resistant Organism or Pan-Drug Resistant Organism within the body of the clinical report.

7.5 Any XDRO or PDRO isolate identified should be reported to public health according to local, regional, and provincial regulations with the additional information outlined in 7.2.

7.6 The originating laboratory should retain the XDRO or PDRO isolates for at least six months, or as required by provincial or local regulations.

7.7 The reference (provincial) laboratory should report all of the data to the National Microbiology Laboratory as defined in 7.2.

Acknowledgements

The subcommittee would like to acknowledge the work of Dr. John Conly (University of Alberta), Dr. Charles Frenette (McGill University), and all the other members of the Canadian Infectious Disease Steering Committee Antimicrobial Resistance Surveillance Task Group. We also appreciate the support of Dr. George Zhanel (University of Manitoba) of the Canadian Antimicrobial Resistance Alliance for feedback on earlier versions of the document. We thank members of the Canadian Public Health Laboratory Network Laboratory Director's Council for review and final approval of the document. We would also like to thank Ms. Sandra Radons-Arneson from our secretariat for her support.

Conflict of interest

None.

Funding

This work was supported in kind by all laboratories of the authors and the Canadian Public Health Laboratory Network Antimicrobial Resistance Subcommittee.

References

1. Laupland KB, Parkins MD, Church DL, Gregson DB, Louie TJ, Conly JM, Elsayed S, Pitout JDD. 2005. Population-based epidemiological study of infections caused by carbapenem-resistant Pseudomonas aeruginosa in the Calgary Health Region: importance of metallo-beta-lactamase (MBL)-producing strains. J Infect Dis 192:1606–1612.
2. Mataseje LF, Bryce E, Roscoe D, Boyd DA, Embree J, Gravel D, Katz K, Kibsey P, Kuhn M, Mounchili A, Simor A, Taylor G, Thomas E, Turgeon N, Mulvey MR, Canadian Nosocomial Infection Surveillance Program. 2012. Carbapenem-resistant Gram-negative bacilli in Canada 2009-10: results from the Canadian Nosocomial Infection Surveillance Program (CNISP). J Antimicrob Chemother 67:1359–1367.
3. Tien HC, Battad A, Bryce EA, Fuller J, Mulvey M, Bernard K, Brisebois R, Doucet JJ, Rizoli SB, Fowler R, Simor A. 2007. Multi-drug resistant Acinetobacter infections in critically injured Canadian forces soldiers. BMC Infect Dis 7:95-2000.
4. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL. 2012. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 18:268-281.
5. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing: Twenty-Third Informational Supplement M100-S25. CLSI, Wayne, PA, USA, 2015.
6. Mosby's Medical Dictionary 9th ed 2012 St. Louis, MO: Mosby Elsevier.
7. Leclercq R, Canton R, Brown DFJ, Giske CG, Heisig P, MacGowan AP, Mouton JW, Nordmann P, Rodloff AC, Rossolini GM, Soussy CJ, Steinbakk M, Winstanley TG, Kahlmeter G. 2013. EUCAST expert rules in antimicrobial susceptibility testing. Clin Microbiol Infect 19:141–160.

Appendix 1

Methodology for Developing the Recommendations

The article published by Magiorakos and colleagues (2012) was used as the main reference for the development of these Canadian recommendations. Drs. German and Mulvey developed the initial framework for the document, which was reviewed by the Canadian Public Health Laboratory Network (CPHLN) AMR Working Group members and invited collaborators. Two main considerations were discussed by the working group members: (i) formulation of a recommendation that focused on antimicrobial drugs commonly used in Canada; and (ii) creation of a document that is easy to use by frontline laboratories, which predominantly utilize automated methods for generating antimicrobial susceptibility data.

Three rounds of discussion and document revision took place with the working group. This included discussion and suggestions from the Communicable and Infectious Disease Steering Committee (CIDSC) AMR Task Group from the Pan-Canadian Public Health Network. The final draft recommendations were reviewed by the CPHLN Executive.

Major variation with recommendations in this document as compared to Magiorakos et. al. (2012) was as follows:

1. The working group decided to focus on Gram-negative isolates to keep the recommendations straightforward and achievable. It was decided that recommendations for Gram-positive organisms would be addressed in a future document;
2. *Stenotrophomonas maltophilia* was added as an additional Gram-negative organism to be considered for the reporting of MDRO, XDRO and PDRO in the Canadian document;
3. Although the definition of MDRO in Gram-negative organisms is an important consideration, given the treatment complications that can be associated with these infections, it was decided at a provincial and national level to voluntarily report only XDRO and PDRO isolates and use the identification of an MDRO as a screening test to direct further testing and reporting of resistant isolates. This was done to ensure frontline laboratories could easily report their findings to reference laboratories, or request additional tests of antimicrobial drugs not covered under the frontline antimicrobial drug panel needed to confirm XDRO/PDRO.
4. A great deal of discussion focused on the value of using the definition of resistance, as defined by CLSI (2015), rather than that of non-susceptibility proposed by Magiorakos et. al. (2012). It was decided to use the CLSI definition of resistance based on the main arguments put forward, which were: (i) front-line laboratories may have difficulty analyzing 'intermediate resistance' data in the context of MDRO/XDRO/PDRO; (ii) there were concerns about the reporting of these organisms in relation to public health. A stringent definition of resistance was determined to be the most feasible solution.
5. It was noted that laboratories may have to use FDA breakpoints, which may differ from the CLSI definitions. It was requested in the recommendations that these differences be noted in the report to the reference laboratory.
6. The exhaustive antimicrobial agents listed in the Tables of the Magiorakos et. al. (2012) publication was simplified to reflect the antimicrobial agents commonly used and available in Canada.
7. Ertapenem was removed as a marker for carbapenem resistance in *Enterobacteriaceae*. The specificity of ertapennem is lower than that of meropenem and imipenem and is not commonly used in a clinical laboratory setting.
8. With the exception of *Acinetobacter* spp. and *S. maltophilia*, the tetracyclines were removed from the list of antimicrobials to be considered as they are not frequently tested in frontline laboratories nor are they commonly used to treat serious infections.
9. The Canadian recommendations requested additional clinical information that were not included in the Magiorakos et. al. (2012) publication.

Appendix 2

Reference Laboratory Contact Information

Dr. Linda Hoang
BC Public Health Microbiology & Reference Laboratory,
655 West 12th Avenue,
Vancouver, BC, V5Z 4R4
linda.hoang@bccdc.ca

Dr. Jeff Fuller
Alberta Provincial Laboratory for Public Health,
Alberta Health Services,
2B3.13 WMC, 8440-112 Street,
Edmonton, AB, T6G 2J2
jeff.fuller@albertahealthservices.ca

Dr. Paul Levett
Saskatchewan Disease Control Laboratory,
5 Research Drive,
Regina, SK, S4S 0A4
plevett@health.gov.sk.ca

Dr. Jared Bullard
Cadham Provincial Laboratory,
750 William Avenue,
Winnipeg, MB, R3E 3J7
jared.bullard@gov.mb.ca

Dr. Samir Patel
Public Health Ontario Laboratories,
661 University Avenue, Ste. 1701
Toronto, ON, N5G 1M1
samir.patel@oahpp.ca

Dr. Brigitte Lefebvre
Laboratoire de santé publique du Québec,
Institut national de santé publique du Québec,
20045 chemin Sainte-Marie,
Ste-Anne-de-Bellevue (Québec) H9X 3R5
marc-christian.domingo@inspq.qc.ca

Dr. Gabriel Girouard
Centre Hospitalier Universitaire Dr-Georges-L-Dumont,
330 Avenue Universite,
Moncton, NB, E1C 2Z3
gabriel.girouard@vitalitenb.ca

Dr. David Haldane
Queen Elizabeth II Health Science Centre,
5788 University Avenue,
Halifax, NS, B3H 1V8
david.haldane@cdha.nshealth.ca

Dr. Greg German
Queen Elizabeth Hospital
60 Riverside Drive
Charlottetown, PE C1A 8T5
gjgerman@ihis.org

Robert Needle
Newfoundland Public Health Laboratory,
Dr. L.A. Miller Centre,
100 Forest Road,
St. John's, NL, A1A 3Z9
robert.needle@easternhealth.ca

Dr. Michael Mulvey
National Microbiology Laboratory
1015 Arlington Street
Winnipeg, MB, R3E 3R2
michael.mulvey@phac-aspc.gc.ca

Efficacy and safety of RTS, S/AS01 malaria vaccine

Source: RTS,S Clinical Trials Partnership. **Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial.** Lancet. 2015 Jul 4;386(9988):31-45. doi: 10.1016/S0140-6736(15)60721-8. Epub 2015 Apr 23.

BACKGROUND: The efficacy and safety of the RTS,S/AS01 candidate malaria vaccine during 18 months of follow-up have been published previously. Herein, we report the final results from the same trial, including the efficacy of a booster dose.

METHODS: From March 27, 2009, until Jan 31, 2011, children (age 5-17 months) and young infants (age 6-12 weeks) were enrolled at 11 centres in seven countries in sub-Saharan Africa. Participants were randomly assigned (1:1:1) at first vaccination by block randomisation with minimisation by centre to receive three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20 (R3R group); three doses of RTS,S/AS01 and a dose of comparator vaccine at month 20 (R3C group); or a comparator vaccine at months 0, 1, 2, and 20 (C3C [control group]). Participants were followed up until Jan 31, 2014. Cases of clinical and severe malaria were captured through passive case detection. Serious adverse events (SAEs) were recorded. Analyses were by modified intention to treat and per protocol. The coprimary endpoints were the occurrence of malaria over 12 months after dose 3 in each age category. In this final analysis, we present data for the efficacy of the booster on the occurrence of malaria. Vaccine efficacy (VE) against clinical malaria was analysed by negative binomial regression and against severe malaria by relative risk reduction. This trial is registered with ClinicalTrials.gov, number NCT00866619.

FINDINGS: 8922 children and 6537 young infants were included in the modified intention-to-treat analyses. Children were followed up for a median of 48 months (IQR 39-50) and young infants for 38 months (34-41) after dose 1. From month 0 until study end, compared with 9585 episodes of clinical malaria that met the primary case definition in children in the C3C group, 6616 episodes occurred in the R3R group (VE 36·3%, 95% CI 31·8-40·5) and 7396 occurred in the R3C group (28·3%, 23·3-32·9); compared with 171 children who experienced at least one episode of severe malaria in the C3C group, 116 children experienced at least one episode of severe malaria in the R3R group (32·2%, 13·7 to 46·9) and 169 in the R3C group (1·1%, -23·0 to 20·5). In young infants, compared with 6170 episodes of clinical malaria that met the primary case definition in the C3C group, 4993 episodes occurred in the R3R group (VE 25·9%, 95% CI 19·9-31·5) and 5444 occurred in the R3C group (18·3%, 11·7-24·4); and compared with 116 infants who experienced at least one episode of severe malaria in the C3C group, 96 infants experienced at least one episode of severe malaria in the R3R group (17·3%, 95% CI -9·4 to 37·5) and 104 in the R3C group (10·3%, -17·9 to 31·8). In children, 1774 cases of clinical malaria were averted per 1000 children (95% CI 1387-2186) in the R3R group and 1363 per 1000 children (995-1797) in the R3C group. The numbers of cases averted per 1000 young infants were 983 (95% CI 592-1337) in the R3R group and 558 (158-926) in the R3C group. The frequency of SAEs overall was balanced between groups. However, meningitis was reported as a SAE in 22 children: 11 in the R3R group, ten in the R3C group, and one in the C3C group. The incidence of generalised convulsive seizures within 7 days of RTS,S/AS01 booster was 2·2 per 1000 doses in young infants and 2·5 per 1000 doses in children.

INTERPRETATION: RTS,S/AS01 prevented a substantial number of cases of clinical malaria over a 3-4 year period in young infants and children when administered with or without a booster dose. Efficacy was enhanced by the administration of a booster dose in both age categories. Thus, the vaccine has the potential to make a substantial contribution to malaria control when used in combination with other effective control measures, especially in areas of high transmission.

The RTS,S/AS01 vaccine continues to show modest protection

Source: Rosenthal PJ. **The RTS,S/AS01 vaccine continues to show modest protection against malaria in African infants and children (Commentary).** Evid Based Med 2015;20:179 doi:10.1136/ebmed-2015-110231.

Malaria remains one of the greatest infectious burdens in the world. The RTS,S vaccine results from decades of research showing that human responses to the *Plasmodium falciparum* circumsporozoite protein can protect against malaria. Vaccine developments benefitted from adjuvant optimisation, with AS01 chosen for recent trials. RTS, S has been extensively studied in African children, with vaccine efficacy approximately 25–50% against both symptomatic and severe malaria, but efficacy lower in infants than in children and waning over time after immunization.

Evaluation of anthrax vaccine safety in 18-20 year olds

Source: King JC Jr, Gao Y, Quinn CP, Dreier TM, Vianney C, Espeland EM. **Evaluation of anthrax vaccine safety in 18 to 20 year olds: A first step towards age de-escalation studies in adolescents.** Vaccine. 2015 May 15;33(21):2470-6. doi: 10.1016/j.vaccine.2015.03.071. Epub 2015 Apr 5.

BACKGROUND/OBJECTIVES: Anthrax vaccine adsorbed (AVA, BioThrax(®)) is recommended for post-exposure prophylaxis administration for the US population in response to large-scale Bacillus anthracis spore exposure. However, no information exists on AVA use in children and ethical barriers exist to performing pre-event pediatric AVA studies. A Presidential Ethics Commission proposed a potential pathway for such studies utilizing an age de-escalation process comparing safety and immunogenicity data from 18 to 20 year-olds to older adults and if acceptable proceeding to evaluations in younger adolescents. We conducted exploratory summary re-analyses of existing databases from 18 to 20 year-olds (n=74) compared to adults aged 21 to 29 years (n=243) who participated in four previous US government funded AVA studies.

METHODS: Data extracted from studies included elicited local injection-site and systemic adverse events (AEs) following AVA doses given subcutaneously at 0, 2, and 4 weeks. Additionally, proportions of subjects with ≥4-fold antibody rises from baseline to post-second and post-third AVA doses (seroresponse) were obtained.

RESULTS: Rates of any elicited local AEs were not significantly different between younger and older age groups for local events (79.2% vs. 83.8%, P=0.120) or systemic events (45.4% vs. 50.5%, P=0.188). Robust and similar proportions of seroresponses to vaccination were observed in both age groups.

CONCLUSIONS: AVA was safe and immunogenic in 18 to 20 year-olds compared to 21 to 29 year-olds. These results provide initial information to anthrax and pediatric specialists if AVA studies in adolescents are required.

Single dose tetravalent dengue vaccine

Source: Durbin AP, Kirkpatrick BD, Pierce KK, Carmolli MP, Tibery CM, Grier PL, et al. **A 12-month interval dosing study in adults indicates that a single dose of the NIAID tetravalent dengue vaccine induces a robust neutralizing antibody response.** J Infect Dis. 2016 Feb 16. pii: jiw067.

The ideal dengue vaccine will provide protection against all serotypes of dengue virus and will be economical and uncomplicated in its administration. To determine the ability of a single dose of live-attenuated tetravalent dengue vaccine TV003 to induce a suitable neutralizing antibody response, a placebo-controlled clinical trial was performed in 48 healthy adults who received two doses of vaccine or placebo administered 12 months apart. Evaluation of safety, vaccine viremia, and neutralizing antibody response after each dose indicated that the first dose of vaccine was capable of preventing infection with the second dose, thus indicating that multiple doses are unnecessary.

Upcoming

April 18–20, 2016. 19th Annual Conference on Vaccine Research. Baltimore, MD, USA. http://www.cvent.com/events/19th-annual-conference-on-vaccine-research/event-summary-9c2a6b5301a64921afbd9c07a4cffa14.aspx?refid=spcoc

June 13–16, 2016. Public Health 2016. Canadian Public Health Association Conference. Toronto, ON. http://www.cpha.ca/en/conferences/conf2016.aspx

July 18–22, 2016. 21st International AIDS Conference (AIDS 2016). Durban, South Africa. http://www.aids2016.org/

CCDR
CANADA COMMUNICABLE DISEASE REPORT

Public Health Agency of Canada
130 Colonnade Road
Address Locator 6503B
Ottawa, Ontario K1A 0K9
ccdr-rmtc@phac-aspc.gc.ca

To promote and protect the health of Canadians through leadership, partnership, innovation and action in public health.

Public Health Agency of Canada

Published by authority of the Minister of Health.

© Her Majesty the Queen in Right of Canada, represented by the Minister of Health, 2016

This publication is also available online at

http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/16vol42/index-eng.php

Également disponible en français sous le titre :
Relevé des maladies transmissibles au Canada